

MODULATION OF AIRFLOW-CONTROLLING MECHANISMS IN NEWBORN
INFANTS BREATHING CARBON DIOXIDE

By

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SYMBOLS AND ABBREVIATIONS

CIA	Central inspiratory activity
CII	Central inspiratory inhibitory
CO ₂	Carbon dioxide
CPG	Central pattern generator
Di	Diaphragm
EEV	End-expiratory volume
EMG	Electromyogram
f	Frequency
Ic	Intercostal
inspDI	Average inspiratory activity of the diaphragm
inspIC	Average inspiratory activity of the intercostal muscles
inspPCA	Average inspiratory activity of the posterior cricoarytenoid muscles
MTA	Moving-time average
PCA	Posterior cricoarytenoid muscle
PCAb	Baseline expiratory activity of the posterior cricoarytenoid muscles
PIIA	Post-inspiratory inspiratory activity
PIIAdi	Post-inspiratory inspiratory activity of the diaphragm
pk $\dot{V}_e$	Peak expiratory flow rate
pk $\dot{V}_i$	Peak inspiratory flow rate
PSR	Slowly adapting pulmonary stretch receptor
r	Correlation coefficient
RAR	Rapidly adapting receptor

TA	Thyroarytenoid muscle
Te	Expiratory time
Ti	Inspiratory time
TPIIAdi	Duration of post-inspiratory inspiratory activity of the diaphragm
TTSS	Time to reach steady-state
UA	Upper airway
$\bar{V}_e$	Mean expiratory flow rate
$\bar{V}_i$	Mean inspiratory flow rate
$\dot{V}_{min}$	Minute ventilation
Vt	Tidal volume

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The effects of carbon dioxide inhalation on the breathing pattern and on mechanisms that control this breathing pattern in the neonate are investigated in this dissertation. Diaphragm, intercostal and posterior cricoarytenoid muscle activities were measured along with respiratory airflow and volume changes in eight full-term newborn infants.

Infants breathing room air exhibited breathing patterns with varying degrees of inspiratory pump and laryngeal muscle activities. Diaphragmatic airflow retardation (braking) during early expiration was observed in six of eight infants. A mixture of 2-3% carbon dioxide in room air was used as a stimulus, and a steady-state response was measured during the fourth minute of the stimulus. The observed breathing patterns with carbon dioxide were qualitatively similar to those during room-air breathing. Tidal volumes were elevated with little change in frequency of breathing, resulting in an average 38% increase in minute ventilation.

Breathing carbon dioxide augmented inspiratory muscle activity of the posterior cricoarytenoids (44%), the intercostals (17%) and the diaphragm (11%). The relative responses of these muscles varied greatly between individuals. No respiratory abdominal muscle activity was recorded at any time during the experiments. Breathing carbon dioxide did not change diaphragmatic post-inspiratory inspiratory activity, but elevated expiratory posterior cricoarytenoid muscle activity to a degree (40%) similar to that of the inspiratory activity.

These experiments contribute important information on respiratory control in the neonate, including 1) the newborn infant adopts varied breathing strategies to defend absolute lung volume including the braking of expiration with the diaphragm and laryngeal muscles, 2) the newborn has the ability to augment minute ventilation in a variety of ways when challenged with carbon dioxide, 3) improving diaphragm-ribcage coupling through intercostal muscle activation may provide an energy-efficient means of enhancing pump muscle performance, 4) the defense of absolute lung volume is of critical importance to the newborn as demonstrated by the persistence of diaphragmatic braking of expiration throughout this chemical challenge, and 5) the modulation of laryngeal resistance to airflow by posterior cricoarytenoid activation plays a crucial role in the ability of the newborn to respond to a chemical load while maintaining absolute lung volume.

CHAPTER 1 INTRODUCTION

The purpose of this study is to investigate the effects of CO_2 inhalation on the breathing pattern and mechanisms that control this pattern in the neonate. The respiratory control system in newborns differs from that of adult humans and other mammalian species. In some ways the newborn is more similar to mammalian species other than human, and much investigation into the respiratory control system of different mammalian species has been performed. It is preferable to study the human neonate itself, when possible, rather than to make inferences from an animal model. Only in this manner can questions about the human infant be unequivocally answered.

The effects of chemical stimulation on reflex modulation of airflow-controlling mechanisms are investigated in the newborn infant. Specifically, experiments are designed to study both transient and steady-state responses to carbon dioxide (CO_2) inhalation as they affect posterior cricoarytenoid (PCA) muscle activity, pump muscle activity (diaphragm and inspiratory intercostals) and airflow pattern in the healthy newborn infant while asleep. This includes the effects of CO_2 inhalation on inspiratory PCA activity, on pump muscle activities, and on expiratory braking mechanisms in newborn infants.

This research shows how a chemical factor shapes the respiratory pattern in the unanesthetized sleeping infant, and it provides useful information on neuromuscular strategies employed by newborn infants to maintain minute ventilation ($\dot{V}_{min}$) and absolute lung volume. Indeed, many of the life-threatening breathing disorders faced by the neonate involve changes in the control of breathing studied in this dissertation. To better understand the genesis of disordered breathing, one must first define the mechanisms controlling respiration in the normal developing infant.

A review of the literature relating to hypercapnia and the control of respiration is presented in Chapter 2. This is followed by studies of the response of newborns to inhaled CO_2 . Effects of this stimuli on inspiration and expiration are treated separately in Chapters 3 and 4, respectively. The final chapter addresses the integration of the inspiratory and expiratory results into a description of the response of the newborn to CO_2 inhalation. Additionally, the relationship of these results to previously proposed models of respiratory control, and speculations on mechanisms underlying the observed responses, are discussed.

CHAPTER 2 LITERATURE REVIEW

The control of breathing in newborns differs from that in adult humans and animals (101,99). Maturational changes in chemical control, mechanical reflexes and the central integrative abilities of the respiratory neuronal network have been observed but are inadequately understood. Behavioral states and respiratory reflexes have been studied for many years, but the integration of these two areas of research is recent. The majority of the speculation on respiratory control mechanisms employed by babies comes from animal studies. These studies often use invasive techniques, and correlations to the control system in the infant are uncertain due to effects of anesthesia (40,53,92,103), relative maturation, and possible species variation.

Sleeping infants, unlike adults, exhibit a eupneic breathing strategy to defend absolute lung volume (36,62,63,73,98). Newborn infants have a highly compliant chest wall that aids in parturition (42), but results in a low relaxation volume (10-15% of total lung capacity as compared to 30-35% for the supine adult). Breathing from this low lung volume could result in decreased oxygen stores (35) and put the infant at risk of small airway closure that may result in atelectasis of terminal lung units. The newborn normally adopts a

breathing strategy to compensate for this mechanical disadvantage by establishing an end-expiratory lung volume (EEV) above the relaxation volume. The newborn can defend EEV by shortening expiratory time (T_e) and/or by actively braking expiration to retard expiratory airflow. By shortening T_e , expiration is normally interrupted before relaxation volume is reached. Methods of braking expiration include dynamic narrowing of the upper airways (UA) and post-inspiratory inspiratory muscle activity (PIIA) (43,66). Evidence suggests that there is an integrative neural mechanism that modulates T_e which is sensitive to both EEV and the rate of lung deflation (59). By retarding expiratory airflow, the rate of lung deflation is decreased and T_e is prolonged. The net effect of braking on EEV depends on the interaction between the mechanical effect to elevate EEV and the opposing effect of T_e prolongation.

There is little information available on the spontaneous occurrence of braking and its neuromechanical consequences in infants. Radvanyi-Bouvet et al. (80) studied expiratory patterns in normal full-term and preterm infants and found that expiration was frequently retarded or airflow was interrupted, but they did not make direct observations of specific braking mechanisms. It appears that even during periods of regular breathing, infants use PIIA early in expiration to oppose rapid emptying of the lungs, and that some degree of UA braking provides a variable, controlled resistance to airflow throughout expiration.

It has been suggested that an important function of the larynx may be to brake expiration to provide an optimal resting respiratory frequency without an end-expiratory pause (81). In the event of an

increase in ventilatory needs, the brake could be removed to provide lower resistance and increased ventilation. There is recent evidence that normal adults use their larynx in this manner. The normal pattern of vocal cord movement in the adult consists of a slight increase in laryngeal resistance during expiration due to vocal cord adduction (28). This expiratory narrowing in adults does not result in an EEV above functional residual capacity as observed in infants. England and Bartlett (27) found that this expiratory laryngeal braking is reduced during hypercapnia and exercise in normal adults. It is reasonable to assume that the newborn infant uses the larynx to control airflow when challenged by chemical loads, as well.

The breathing strategy employed by the newborn infant to increase ventilation during CO_2 inhalation is quite variable and different from that used by the adult. The adult shortens both inspiratory time (T_i) and T_e and increases tidal volume (V_t) during CO_2 inhalation (39). The response of infants breathing CO_2 appears to depend on sleep state and gestational age. Several groups of investigators have studied the effect of CO_2 inhalation on ventilatory parameters in full-term infants, and have arrived at different conclusions. All investigators agree that there is a marked increase in minute ventilation with CO_2 inhalation, but there is disagreement as to the contribution of frequency and V_t to this increase. Some investigators found an increase in both V_t and frequency (10,21,52,64,69), others noted an increase in V_t alone (2,22,25,45,94,97), while still others found the response to be quite variable and dependent on sleep state (8,9,84). In addition to these differences, there is debate as to the influence of sleep state on the

magnitude of the ventilatory response to CO_2 . Some investigators have found a reduced ventilatory response to CO_2 in REM sleep (2,15,46,52) while others found similarity in the CO_2 response in REM and NREM sleep (22,32,45). Overall, most investigators have observed an increase in V_t with no timing change due to CO_2 breathing during nonREM sleep.

Studies in premature infants have found that the response to CO_2 is less than in the full-term (64,70,85), but there is disagreement as to how this change in ventilation is mediated and what effect sleep state has on the CO_2 response. Some investigators have found that both frequency and V_t contribute to the ventilatory response (21,22,24,26,85). Others have found only an increase in V_t (10,37,64,86,87). Others, still, have found the response to be variable and dependent on sleep state, breathing pattern, or time course of the stimulus (8,9,55,67). Two things that all investigators appear to agree on is that there is a graded increase in ventilation with increasing inspired CO_2 concentration, and that premature infants respond less than full-term infants.

Investigations to elucidate the mechanisms responsible for the increase in ventilation with CO_2 inhalation have led to the recording of the activity of respiratory pump muscles and airflow-controlling muscles during CO_2 inhalation in babies. There is an increase in pump muscle activity during CO_2 inhalation (17,46,84), and an increase in activity of two upper airway dilating muscles (17,88), the alae nasi and genioglossus muscles. Since the larynx has been implicated as a primary site for airflow control, the response to CO_2 of the principal

laryngeal abductors, the PCA muscles, should be examined along with their interaction with pump muscle activation during CO_2 inhalation.

The mechanisms responsible for changes in the ventilatory pattern of the neonate due to CO_2 breathing are not fully understood. Experiments performed on animal models allow more invasive techniques to be used to examine the respiratory control system, and to this end, models have been proposed and tested. It is difficult to relate decerebrate or vagotomized animals to sleeping infants, yet these animal studies form a framework on which a general model describing the mechanisms controlling neonatal respiration can be built. The following studies examine the mechanisms responsible for the ventilatory pattern of the sleeping neonate and how these mechanisms are influenced by CO_2 breathing.

CHAPTER 3
INSPIRATORY LARYNGEAL AND PUMP MUSCLE ACTIVITIES DURING
CO₂ BREATHING IN NEONATES

The ventilatory response of the term infant to inspired CO₂ during quiet sleep consists of increased tidal Vt with no change in frequency (2,22,25,45), resulting in increased flow rates. These increased flows can be achieved by increasing the activity or effectiveness of the respiratory pump, or by decreasing resistance to airflow. In premature (16,17) and term infants (61), as well as adults (76,77,96), the UA muscles are activated in synchrony with respiration and are critical in modulating airflow. The intrinsic laryngeal muscles produce changes in UA resistance by altering laryngeal caliber in animals (4,6,23) and adult humans (12,13). The paired PCA muscles abduct the vocal cords and exhibit primarily inspiratory burst activity in both adult humans (12,13) and newborn infants (16,61). A lowered resistance to airflow during the inspiratory phase of spontaneous respiration has been well documented in several species, including humans (28).

During CO₂ inhalation, electromyographic studies in premature infants have documented increased diaphragmatic (17,46,84), genioglossus (88), alae nasi (17) and laryngeal (16) muscle activities. The percent increase in minute ventilation during CO₂ breathing is less for the premature infant as compared to the term infant, although both populations exhibit an increased Vt with CO₂

breathing during quiet sleep (10,70). Electromyographic information is lacking in the term infant; thus, experiments were designed to determine the roles of the laryngeal and pump muscles in the ventilatory response of the term neonate to CO_2 inhalation.

Experimental Design and Methods

Subjects

Subjects consisted of 8 healthy term infants with gestational age 39.9 ± 0.4 wk (mean $\pm$ SD), postnatal age 55 ± 23 hr and birthweight 3.4 ± 0.3 kg. Delivery was by cesarean section for 4 subjects and vaginal for the other 4. Four subjects were male and 4 were female. Informed parental consent was obtained, and a pediatrician and nurse were present throughout the studies.

Study Protocol

Studies were performed 1 hour after a feeding when the infant was sleeping supine. The head was turned to one side and in a neutral position with little flexion or extension of the neck. Sleep state was assessed by standard behavioral criteria (79) and confirmed in four subjects by measuring the electrooculogram with gold cup surface electrodes. Subjects were stimulated with a mix of $2.4 \pm 0.4\%$ CO_2 in room air by fixing a bag filled with the gas to the inspiratory port of a two-way valve attached to the facemask. The total deadspace of the system was less than 3 ml.

Studies consisted of at least 2 minutes of room-air breathing followed by at least 4 minutes of CO_2 breathing, with another 2-minute control period after the CO_2 run. Breathing runs were used for analysis if 90% of the computed steady-state ventilatory response was reached (see Data Analysis). The level of CO_2 used for each infant was

determined by the response of that individual. The first run consisted of approximately 3% CO_2 . If the infant was aroused by this mixture, a 2% CO_2 mixture was added to the 3% mixture in the bag to decrease the inspired CO_2 level. Only runs where the subject remained in nonREM sleep throughout the sampling period were included for analysis.

Measurements

Diaphragm, intercostal and abdominal muscle electromyograms (EMGs) were measured with bipolar skin surface electrodes. Diaphragm leads were placed over the sixth and seventh intercostal spaces in the right anterior axillary line. Intercostal leads were placed parasternally over the second or third rib space. Electrodes were placed on the abdomen just to the right of the navel. The PCA muscle EMG was measured with bipolar silver electrodes built into a 5-French infant feeding tube (61). This tube was placed in the esophagus immediately posterior to the larynx where the PCA muscles are located.

A fast-response CO_2 analyzer (Beckman LB-2) with a nasal catheter was used to continuously measure CO_2 concentrations. Airflow and airway pressure were measured using a previously described low-deadspace facemask-pneumotach system (61) and differential pressure transducers (Validyne MP45). Volume was obtained by digitally integrating the flow signal.

Data Analysis

Data were digitized and analyzed using a laboratory computer (DEC LSI-11/23). Muscle EMGs were digitized at a sampling frequency of 1 kHz and all other signals were sampled at 200 Hz. A 100 ms moving time average (MTA) was computed for each EMG after the electrocardiogram artifacts in the diaphragm and intercostal EMGs were subtracted

using the technique of Bloch (7). Values were computed continuously and averaged over 15-second intervals to determine the steady-state response time. The 15-second averages of V_t and $\dot{V}_{min}$ for the time of CO_2 breathing were fitted to the equation $y=a-b\exp(-c*t)$ using a least-squares nonlinear asymptotical regression (Gauss-Newton algorithm) (67). In this equation, a is the steady-state level, $a-b$ is the value at time $t=0$, and c is the rate constant. From this equation, 90% of the computed steady-state response was calculated.

Onset of EMG activity and neural inspiratory time were determined from the MTA for each muscle by computer-assisted detection of increasing and decreasing slope as previously described (61). The mean inspiratory activity of the diaphragm (inspDI), intercostal (inspIC) and PCA (inspPCA) muscles were computed as the area under the corresponding MTA above electrical zero during neural inspiratory time, divided by that time.

Data were combined into 60-second epochs which consisted of 2 control epochs, 4 or 5 epochs of CO_2 breathing and up to 2 control epochs following CO_2 inhalation. To determine statistical differences between epochs, a repeated-measures ANOVA with Tukey's multiple range test was used. Simplifying the ANOVA procedure necessitated taking an equal number of breaths from each epoch. The number of breaths used differed between individuals, but was kept constant within a subject (ranging from 28-46 breaths/epoch). The number of breaths/epoch for a subject equaled the lowest number of breaths in any epoch for that individual. Within an epoch, breaths were chosen from the middle so that an equal number of breaths were eliminated from the beginning and

end of a period. All correlations were determined using a least-squares method. Group correlations were performed on the percent changes in muscle activities and ventilatory parameters ($n=8$ subjects). To analyze the relationship between muscle activities and changes in flow rates within individuals, simple and multiple least-squares linear regressions were performed sequentially on the 15-second period data for 1 minute before and 4 minutes during CO_2 breathing ($n=20$ time periods), for each subject. Mean inspiratory ($\bar{V}_i$) and peak inspiratory ($\text{pk}\dot{V}_i$) flow rates, as well as V_t and $\dot{V}_{\text{min}}$ were used as dependent variables, and EMG data were used as independent variables.

Results

All 8 subjects reached 90% of the computed steady-state ventilatory response by the fourth CO_2 epoch. Times to reach 90% of steady-state were 98 ± 87 s (mean $\pm$ SD) for $\dot{V}_{\text{min}}$ and 110 ± 100 s for V_t . Thus, all subsequent comparisons of CO_2 to control values will refer to the fourth CO_2 epoch. The CO_2 stimulus was sufficient to raise end-tidal CO_2 significantly from a control level of 38.3 ± 1.4 to 40.2 ± 1.3 torr (mean $\pm$ SE). Average values for mechanical variables during room-air and CO_2 breathing are shown in Table 3-1 in absolute units. Table 3-2 lists electromyographic variables in standardized units (percent change) and compares them to standardized mechanical variables. There was no change found in frequency of breathing or respiratory cycle timing, but there was a 42% increase in V_t during CO_2 inhalation (Tables 3-1 and 3-2). The increased V_t resulted in a 38% increase in $\dot{V}_{\text{min}}$. Changes in $\dot{V}_{\text{min}}$ were highly correlated ($r=0.94$, $P<0.001$) with changes in V_t . The augmentation of

TABLE 3-1
Mechanical Variables During Room-Air and CO₂ Breathing

	Room-Air	CO ₂		TTSS (sec)
$\dot{V}_{min}$	230 $\pm$ 22	*318 $\pm$ 30	(ml/min)/kg	98 $\pm$ 31
V_t	5.0 $\pm$ 0.6	*6.9 $\pm$ 0.7	(ml/kg)	110 $\pm$ 35
$\bar{V}_i$	8.5 $\pm$ 0.9	*11.5 $\pm$ 1.0	(ml/sec)/kg	125 $\pm$ 43
$pk\dot{V}_i$	12.3 $\pm$ 1.4	*17.5 $\pm$ 1.6	(ml/sec)/kg	108 $\pm$ 23
f	48 $\pm$ 4	47 $\pm$ 3	(breaths/min)	
T_i	0.58 $\pm$ 0.03	0.60 $\pm$ 0.03	(sec)	
T_e	0.71 $\pm$ 0.07	0.72 $\pm$ 0.06	(sec)	

Values are means $\pm$ SE for the minute preceding and the fourth minute of CO₂ breathing. Significant difference from room-air breathing ($P < 0.05$) indicated with "*".

TABLE 3-2
Inspiratory Electromyographic and Ventilatory Variables

Subject	inspDI	inspIC	inspPCA	$\dot{V}_{min}$	V_t
1	4	29*	108*	74*	91*
2	19*	29*	14	56*	49*
3	17*	26*	66*	53*	67*
4	22*	19*	59*	50*	49*
5	11*	23*	34*	27*	23*
6	6	14*	33*	18*	31*
7	8	-5	15*	18*	21*
8	0	1	24*	15*	11
$\bar{x} \pm SE$	11 $\pm$ 3*	17 $\pm$ 5*	44 $\pm$ 12*	38 $\pm$ 8*	42 $\pm$ 10*
TTSS	94 $\pm$ 9	100 $\pm$ 45	155 $\pm$ 50	98 $\pm$ 31	110 $\pm$ 35

Values are expressed as percent change from room-air breathing. Significant changes ($P < 0.05$) are indicated with "*".

V_t with no change in timing resulted in elevated $\bar{V}_i$ and $pk\dot{V}_i$ (Table 3-1). Changes in $\dot{V}_{min}$ were also highly correlated with increases in flow rates ($r=0.96$ for $pk\dot{V}_i$, $r=0.97$ for $\bar{V}_i$, $P<0.0001$).

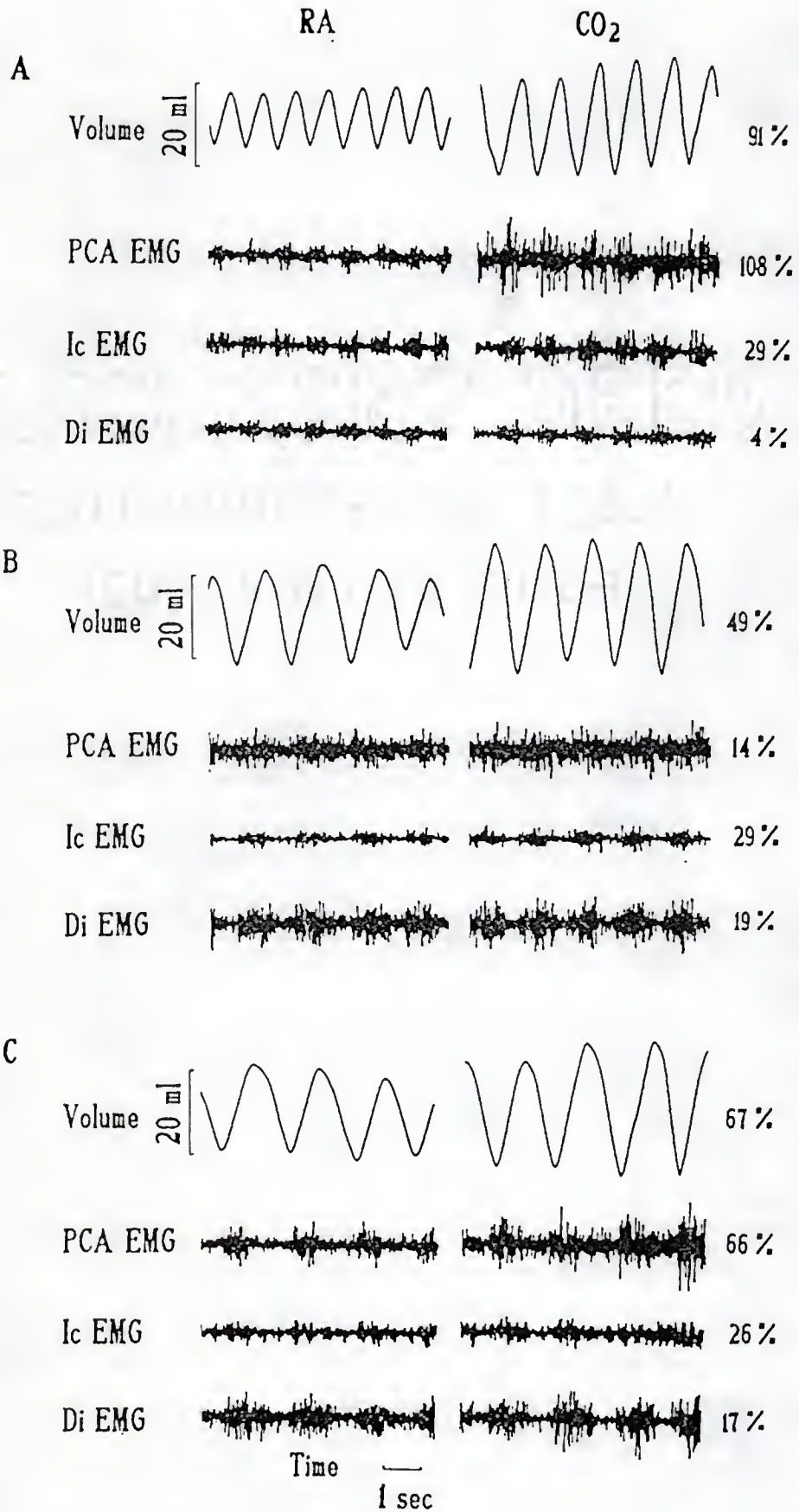
Mean inspiratory pump muscle activities were elevated, with $inspDI$ and $inspIC$ increasing an average of $11 \pm 3\%$ and $17 \pm 5\%$, respectively. Both parameters had a similar rate of rise to reach steady-state (TTSS) as $\dot{V}_{min}$ and V_t (Table 3-2). There was also a large increase in $inspPCA$ ($44 \pm 12\%$) that exhibited a somewhat longer time to reach steady-state (Table 3-2). Activity in phase with respiration was not recorded at any time from the abdominal leads.

The strategy adopted by an individual to increase $\dot{V}_{min}$ varied considerably. Tracings of 3 different strategies are displayed in Figure 3-1; predominantly elevated PCA activity (Panel A), predominantly increased pump muscle activity (Panel B) and increased pump muscle combined with elevated PCA activity (Panel C). As shown in Table 3-2, 4 subjects (nos. 1, 6, 7 and 8) exhibited increased $inspPCA$ with insignificant changes in $inspDI$. Two of these 4 (nos. 1 and 6) also showed increased $inspIC$. One subject (no. 2) only increased $inspDI$ and $inspIC$, and 3 subjects (nos. 3, 4 and 5) increased all inspiratory muscle activities.

Increases in $inspDI$ were significant in 4 subjects (Table 3-2). Thus, group analysis found a weak correlation between $inspDI$ and $\bar{V}_i$ ($r=0.43$, ns) (Figure 3-2). Within individuals, $inspDI$ was correlated ($P<0.05$) with $\bar{V}_i$ in 4 subjects ($r=0.75 \pm 0.06$, mean $\pm$ SD), with $pk\dot{V}_i$ in 5 subjects ($r=0.76 \pm 0.14$), and with V_t in 4 subjects ($r=0.68 \pm 0.10$). An example of an individual regression is illustrated in Figure 3-3.

FIGURE 3-1: Breathing Strategies with CO₂ Breathing.

Representative examples of 3 strategies to increase ventilation during CO₂ breathing (right tracings) as compared to room air (RA) breathing (left tracings). Strategies include increased PCA activity (Panel A, subject 1), increased pump muscle activity (Panel B, subject 2) and increased activity of all muscles (Panel C, subject 3). Shown in each panel are the volume spirogram, PCA EMG, intercostal (Ic) EMG and diaphragm (Di) EMG. Values to the right, starting at the top, are % changes from room-air breathing for Vt, inspPCA activity, inspIc activity and inspDi activity.



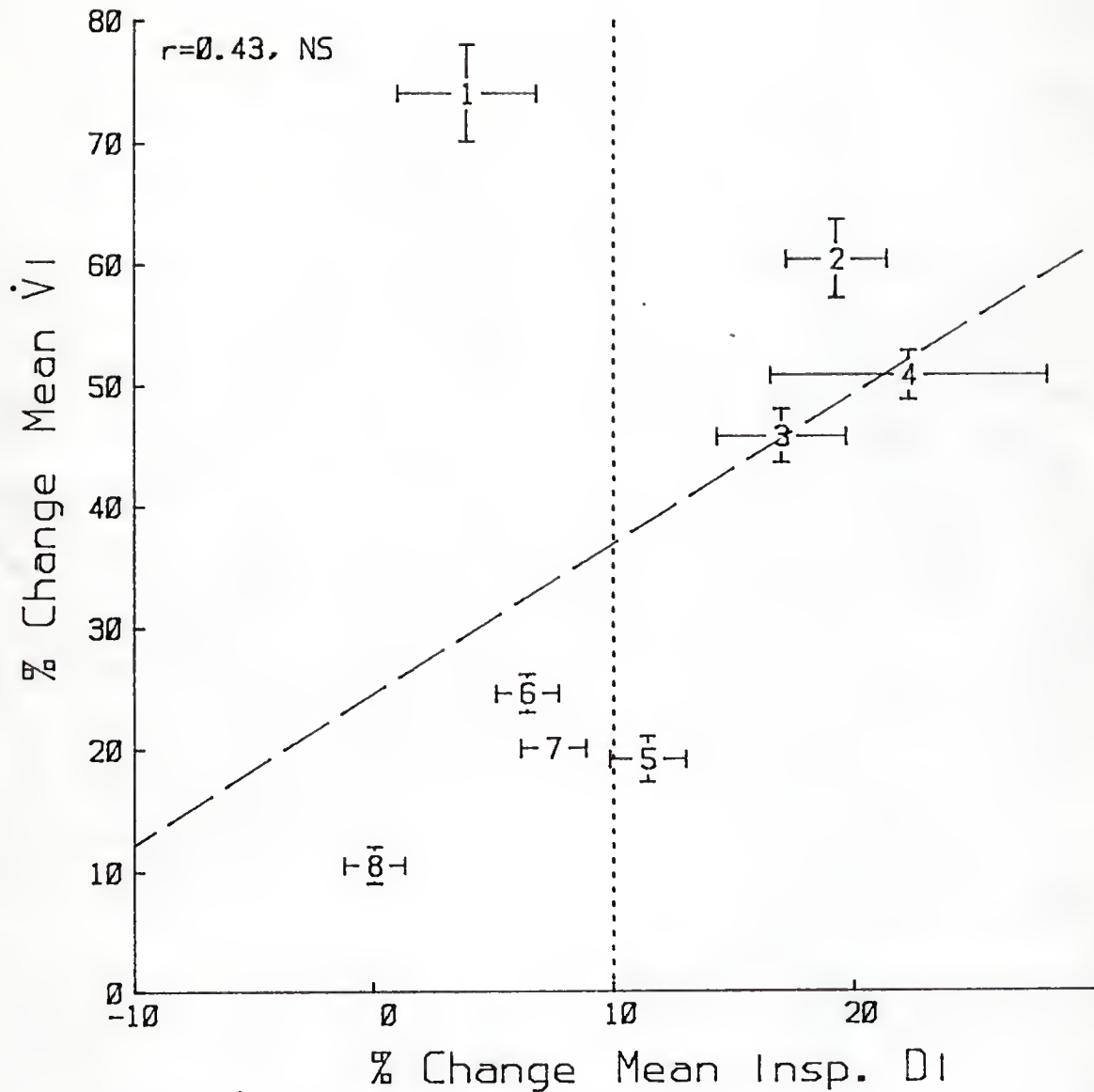


FIGURE 3-2: Airflow and Diaphragm Activity Changes.

Values are expressed as percent change from room-air breathing. Points are mean $\pm$ SE for each of 8 subjects. A regression line is plotted (---) with a correlation coefficient (r). Points right of the vertical line (---) are significantly elevated diaphragm activities ($P < 0.05$). All values for $\dot{V}_I$ are significantly elevated.

Increases in inspIC were significant in 6 subjects (Table 3-2). Group analysis found a good correlation between inspIC and $\bar{V}_i$ ($r=0.77$, $P<0.05$) (Figure 3-4). Within individuals, inspIC was correlated ($P<0.05$) with $\bar{V}_i$ in 4 subjects ($r=0.58 \pm 0.08$), with $pk\dot{V}_i$ in 5 subjects ($r=0.61 \pm 0.10$), and with V_t in 5 subjects ($r=0.61 \pm 0.08$).

When inspPCA was analyzed, 7 subjects exhibited a rise in activity (Table 3-2), and the increased activities were correlated with changes in $\bar{V}_i$ ($r=0.66$, $P<0.05$) (Figure 3-5). Individual regressions found inspPCA correlated ($P<0.05$) with $\bar{V}_i$ in 6 subjects ($r=0.65 \pm 0.14$), with $pk\dot{V}_i$ in 7 subjects ($r=0.69 \pm 0.18$), and with V_t in 7 subjects ($r=0.66 \pm 0.14$).

Multiple regressions were performed within individuals in an attempt to better define changes in inspiratory flow rates. When inspDi, inspIC and inspPCA were combined as independent variables in these regressions, good correlations with $\bar{V}_i$ (range=0.78-0.95, mean= 0.85 ± 0.06 (SD)) and with $pk\dot{V}_i$ (range=0.76-0.95, mean= 0.89 ± 0.07) were found in all 8 subjects.

Discussion

The healthy, term infant in nonREM sleep augmented $\dot{V}_{min}$ during CO_2 breathing by increasing V_t with no change in frequency or timing as previously reported (2,22,25,45). In this study, it was found that the breathing strategy employed by an individual to meet this challenge varied considerably. Large differences in the relative contributions of the various respiratory muscle activities to the hypercapneic response of the present subjects were observed; yet despite these differences, the combinations of muscle activities

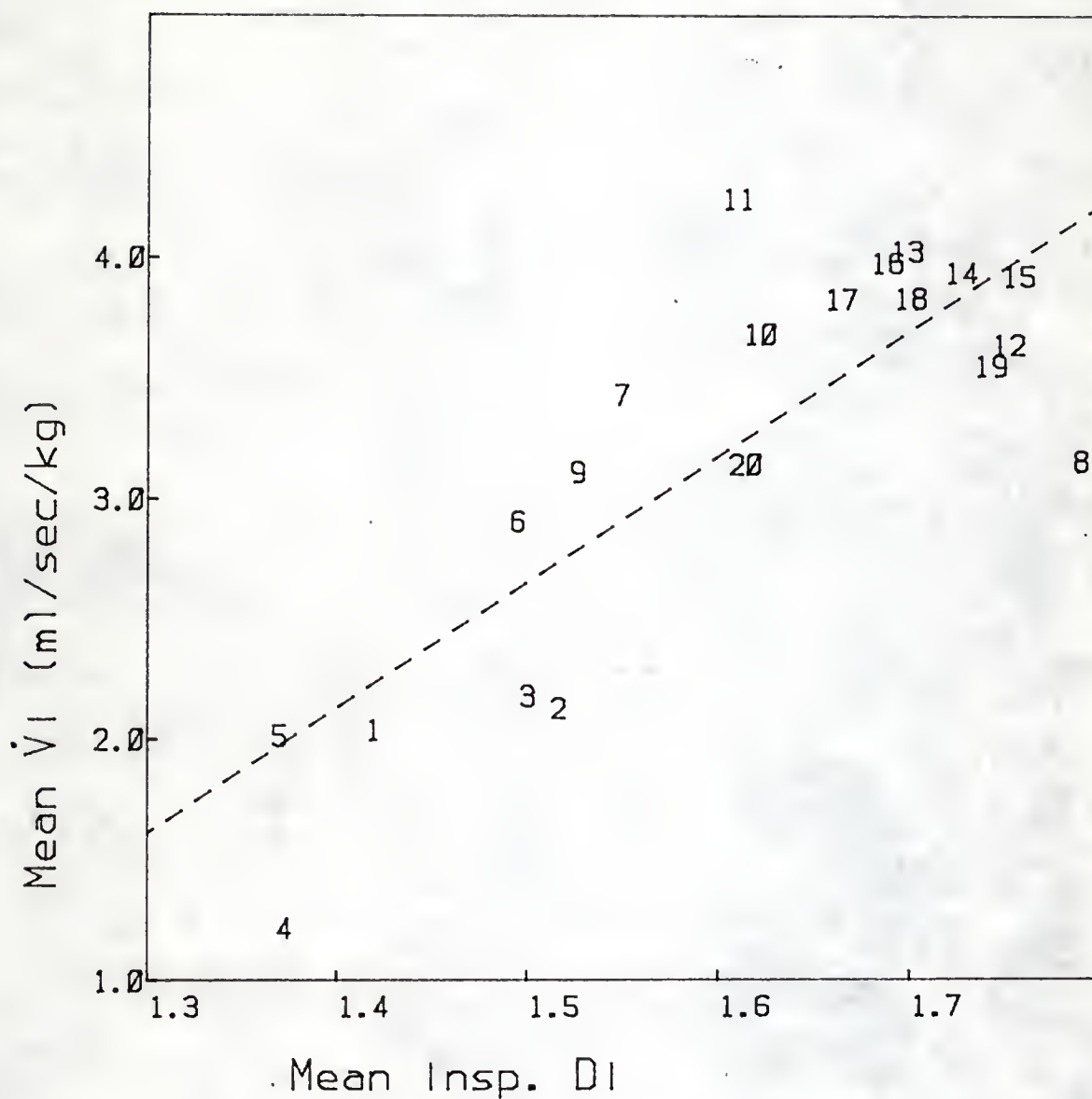


FIGURE 3-3: Example of an Individual Regression.

Data is from Subject 2, showing the relationship between inspDI and $\dot{V}_I$. Points are mean values for successive 15-second intervals starting 1 minute before CO_2 breathing and ending after 4 minutes of CO_2 breathing (20 points total). The correlation coefficient for this regression was 0.83 ($P < 0.0001$).

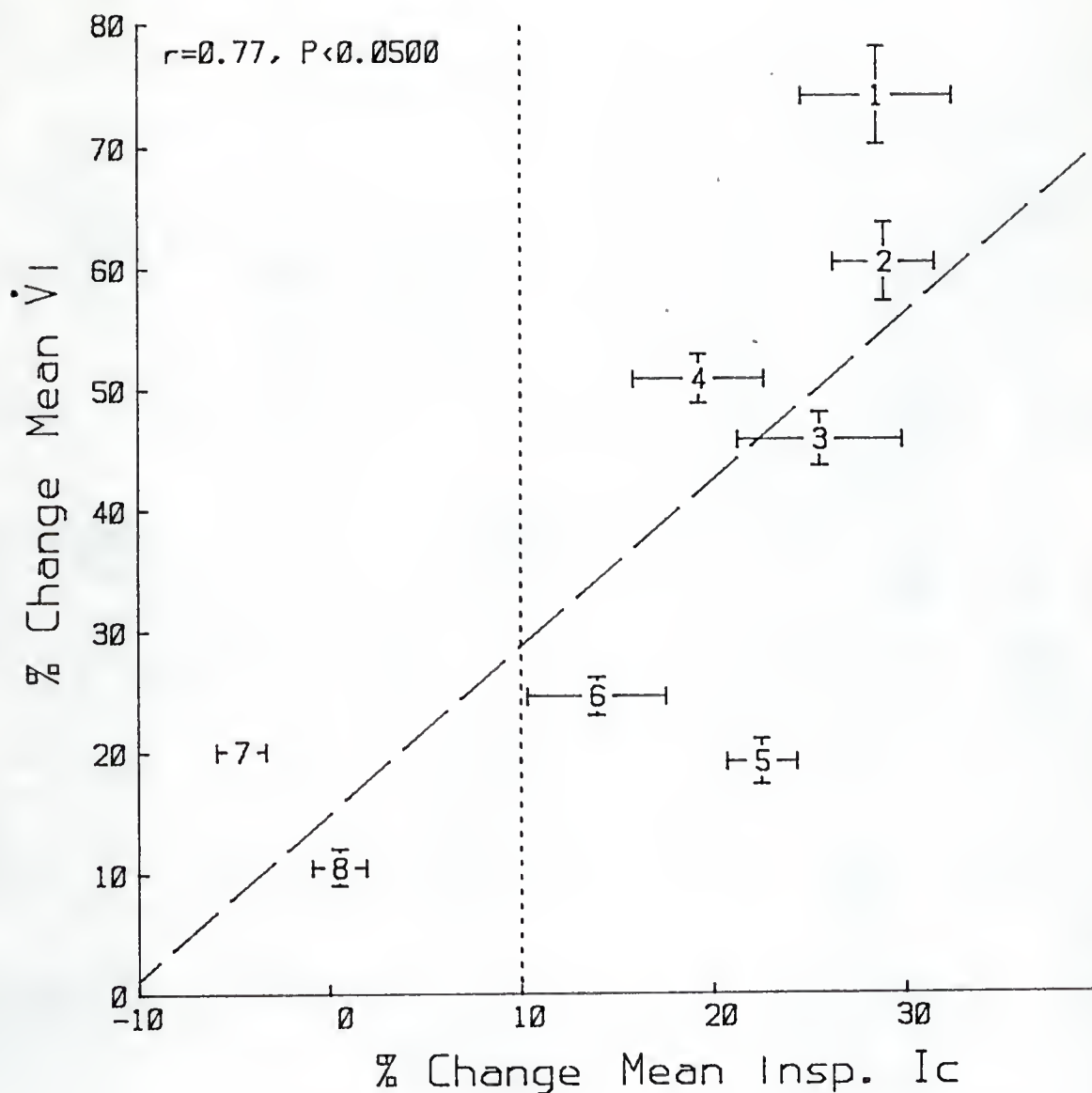


FIGURE 3-4: Airflow and Intercostal Muscle Activity Changes.

Values are expressed as percent change from room-air breathing. Points are mean $\pm$ SE for each of 8 subjects. A regression line is plotted (---) with a correlation coefficient (r). Points right of the vertical line (---) are significantly elevated intercostal muscle activities ($P<0.05$). All values for $\dot{V}_I$ are significantly elevated.

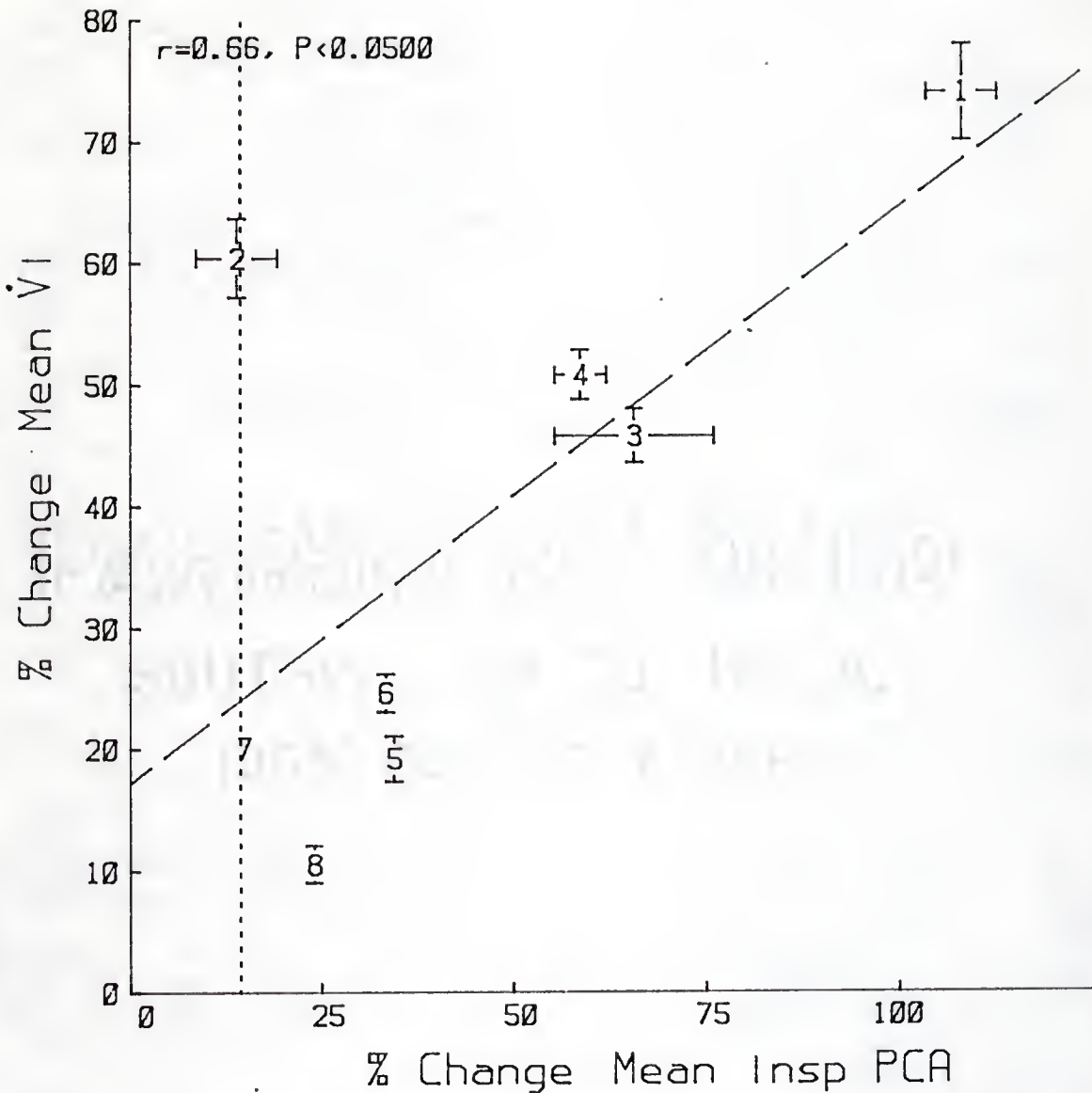


FIGURE 3-5: Airflow and PCA Muscle Activity Changes.

Values are expressed as percent change from room-air breathing. Points are mean $\pm$ SE for each of 8 subjects. A regression line is plotted (---) with a correlation coefficient (r). Points right of the vertical line (---) are significantly elevated PCA muscle activities ($P<0.05$). All values for $\dot{V}_I$ are significantly elevated.

resulted in similar ventilatory responses of increased V_t with no rate or timing change for all subjects.

A change in ventilatory pattern of elevated V_t without timing changes necessitates increased $\bar{V}_i$. Inspiratory airflow can be increased through augmented pump muscle activity and/or decreased UA resistance. An increase in activity of the diaphragm, the primary pump muscle of inspiration, was observed along with increased inspiratory parasternal intercostal muscle activity. Overall, changes in inspIC correlated better with $\bar{V}_i$ than did inspDI , and within individuals, inspIC correlated with V_t in 5 subjects as compared to 4 for inspDI . This is consistent with studies in adult humans where it was observed that the increased V_t during CO_2 breathing was closely linked to recruitment of the rib cage (78) as measured with magnetometers. These data also support the conclusions reached in a study on term infants where it was found that the slope of the CO_2 response curve during rebreathing was determined primarily by rib cage recruitment (52) as measured by respiratory inductive plethysmography. In addition to direct inspiratory action, the increase in inspIC observed may reflect a stiffening of the chestwall to improve mechanical coupling between the diaphragm and rib cage. This would improve the inherent instability of the neonatal chestwall and make the diaphragm a more effective pump (50,66,73). All 4 subjects that increased inspDI with CO_2 breathing also increased inspIC (Table 3-2), but 2 subjects increased inspIC without a significant increase in inspDI (subjects 1 and 6). Thus, increased inspiratory airflow can be achieved with little change in diaphragmatic activation by improving coupling of the diaphragm and rib cage. Additionally, this suggests that augmented

intercostal muscle activation is necessary for increased inspDI to be effective in elevating V_t .

Increased inspPCA is well correlated with inspiratory flow (Figure 3-5). This suggests active laryngeal dilation during CO_2 breathing in most subjects. This is consistent with observed increases in the activity of UA muscles with hypercapnia in animals (5,6,29,49,91) and adult humans (12,13,76,77,96), as well as infants. Specifically, investigators have observed increased genioglossus activity in term infants (88) and elevated alae nasi (17) and laryngeal muscle (PCA) activities (16) in premature infants with hypercapnia. In the present study an increase in measured PCA activity of 44% was found. This is more than twice the increase in pump muscle activity (11 and 17%), and is consistent with the animal and adult human data. Carlo et al. (16) observed that peak diaphragmatic activity increased 50% and peak laryngeal EMG increased 142% in premature infants breathing 4% CO_2 in room air. The relatively larger response of the PCA muscles to CO_2 breathing, in addition to a more consistent correlation with inspiratory flow, suggests that control of laryngeal caliber plays a vital role in elevating inspiratory airflow rates in the newborn. To meet an increased ventilatory demand, tapping the intrinsic flow reserves afforded by baseline laryngeal caliber provides an efficient means to bring about increased inspiratory airflow, thus sparing the inspiratory pump muscles.

A striking feature of this study was the variation found in breathing strategies employed by individuals in response to CO_2 challenge, perhaps reflecting an immature respiratory control system. Subject no. 1 had the largest increase in V_t and greatest ventilatory

response (Table 3-2). Little change in inspDI was observed, while this infant had the largest increases in inspIC and inspPCA (Figure 3-1, Panel A). Thus, a combination of increased chestwall stability and active laryngeal dilation, without a significant increase in inspDI, appeared to be more than adequate to significantly increase V_t and $\dot{V}_{min}$ in this individual. This is illustrated in Figures 3-2, 3-4, and 3-5, where what appears to be an inadequate diaphragmatic response of subject no. 1 (Figure 3-2) is offset by large increases in inspIC (Figure 3-4) and inspPCA (Figure 3-5).

Infant no. 2 had the third largest increase in V_t and the second greatest increase in $\dot{V}_{min}$. Little change was observed in PCA activity in this individual (Figures 3-1, Panel B, and 3-5), which may reflect a lack of active laryngeal dilation in response to CO_2 . Alternatively, although one cannot determine this from these results, one would not expect a large increase if laryngeal caliber was near maximum prior to the hypercapneic stimulus. In Figure 3-2 it can be seen that, despite a small PCA response (Figure 3-5), subject no. 2 elevated $\bar{V}_i$ 60%. This was accomplished by increasing inspDI and inspIC 19% and 29% (Figures 3-2 and 3-4), respectively. This suggests an additive effect of diaphragmatic and intercostal activity in increasing V_t and augmenting $\dot{V}_{min}$.

Subject no.3 exemplifies a strategy of shared contributions from all three muscle groups (Figures 3-1, Panel C, 3-2, 3-4, and 3-5) to meet the CO_2 challenge, resulting in the second largest increase in V_t and the third greatest increase in $\dot{V}_{min}$. Data from the remaining 5 subjects also show variability in individual breathing strategies in response to hypercapnia.

The breathing strategy employed by a subject to respond to the CO_2 challenge may be predetermined by that subject's baseline room-air breathing strategy. This baseline strategy also varies between individuals. Particularly, the laryngeal caliber during room-air breathing directly effects the degree to which further dilation is possible. It is conceivable that in healthy infants, and more so in infants with respiratory disease, the response of the inspiratory pump muscles is predetermined by their corresponding baseline activities. Substantial activation during room-air breathing would limit the potential response of that muscle to the chemical load.

One would assume that the healthy infant would have flow reserves afforded by the baseline activity of both UA and inspiratory pump muscles. Submaximal baseline PCA activity associated with submaximal laryngeal caliber would allow increased activation to utilize this flow reserve during times of increased ventilatory demands. Likewise, the pump muscles could also be augmented in this fashion.

The baseline and stimulated activities of UA and pump muscles may be influenced by mechanical factors. In subjects with good mechanical coupling of the ribcage and diaphragm, one might expect proportional responses of all the muscles to an applied chemical load. In subjects with poor mechanical coupling, two possible baseline strategies may be employed that in turn may effect that subject's potential CO_2 response. A baseline breathing strategy of augmented pump muscle activity to compensate for existing chestwall instability may limit further increases in pump muscle activities in response to an added chemical load. Thus, this individual may exhibit a

substantial increase in PCA activity to decrease UA resistance and increase airflow during the CO₂ challenge. Alternatively, an infant with a baseline breathing strategy of increased PCA activity to allow greater flow rates in the face of existing chestwall instability may have no alternative but to increase pump muscle activation when faced with a chemical load. These two scenarios are extreme cases, and of course, a variety of baseline breathing strategies composed of varying contributions of the pump and UA muscles are observed. Thus, a variety of response strategies are also found.

The results of this study in healthy infants may provide useful information for a better understanding of the mechanisms employed by sick infants attempting to compensate for abnormalities associated with respiratory disease. Very high ventilatory demands are often associated with respiratory disease. The UA may be critical in modulating airflow in cases involving low lung compliance where the inspiratory pump muscles are considerably loaded.

A similar correlation can be drawn with premature infants where shape instability of the ribcage is prominent and varies with maturity. Premature infants may depend on UA mechanisms to adjust airflow resistance when confronted with ventilatory demands in an effort to spare pump muscles that are operating at a mechanical disadvantage. Additionally, these infants may be highly dependent on increases in inspIC to meet respiratory challenges while minimizing further ribcage distortion.

Overall, the importance of combined increases of inspIC and inspPCA with chemical loading cannot be overemphasized. Minimizing paradoxical rib cage movement may be crucial in sparing the primary

inspiratory pump muscle additional work. The present results support the idea that intercostal muscle recruitment to stabilize the ribcage plays an important role in the response to CO_2 in the neonate. In fact, the small change in inspDI measured may actually be overestimating diaphragmatic activation due to contamination of the signal by lower inspiratory intercostal muscle activity. Augmented inspPCA, suggesting active laryngeal dilation, provides a cost-effective way to elevate inspiratory flow rates, and additionally spares the primary pump muscle.

In summary, the response of the newborn to CO_2 inhalation depends on the coordinated activation of the diaphragm, intercostal muscles, and laryngeal muscles to bring about increased V_t with little change in respiratory cycle timing. The relative contributions of these muscles to a common ventilatory response varies greatly, although PCA and intercostal muscle activity consistently exhibited a higher correlation than the diaphragm with changes in V_t and inspiratory flow rates. In conclusion, the newborn infant is able to use a variety of breathing strategies to augment V_t and $\dot{V}_{\text{min}}$ during times of increased ventilatory demands.

CHAPTER 4
MUSCLE ACTIVITIES RELATED TO EXPIRATORY AIRFLOW
DURING CO₂ BREATHING IN NEONATES

Resistance to airflow is higher during expiration than during inspiration, coinciding with laryngeal narrowing as described in both animals (4,6) and adult humans (13,28). Augmenting expiratory airflow resistance may play an important role in defending absolute lung volume in the newborn infant who is at a mechanical disadvantage at birth due to a highly compliant chest wall (42). The term neonate adopts a breathing strategy to establish EEV above an intrinsically low relaxation volume by retarding (braking) expiratory airflow (59,63,71,72).

Methods of braking expiratory airflow include PIIA, which opposes passive lung recoil during early expiration, and dynamic UA narrowing, which increases resistance to expiratory airflow. Electromyographic evidence of PIIA, specifically PIIA of the diaphragm (PIIA_{di}), has been obtained from studies of both premature (17,66,95) and term infants (63). The braking of expiratory airflow using UA narrowing in addition to PIIA is known to occur in newborn animals (29,47,48,51). An airflow pattern of UA braking is also seen in newborn humans and activation of the thyroarytenoid (TA) muscles, laryngeal adductors, has been implicated as the mechanism responsible for the reduced airflow (36,71,80). In fact, there is no direct evidence of adductor activity in infants, but recordings of

PCA muscle activity in both premature and term infants using an esophageal electrode have correlated reduced abductor activity with a retardation of expiratory airflow (16,61). This is similar to the pattern seen in the newborn opossum (33) and most adult animals (6,48) and humans (12).

Radvanyi-Bouvet et al. (80) studied expiratory patterns in normal full-term and preterm infants and found that expiration was frequently retarded or airflow was interrupted, but they did not make direct observations of specific braking mechanisms. Expiratory patterns in full-term infants were recently categorized and correlated with diaphragm and PCA electromyograms providing clear evidence of PIIAdi and illustrating the important role of intrinsic laryngeal muscles in providing controlled braking of expiration in the sleeping neonate (61). These patterns included 1) expiratory braking with PIIAdi, 2) expiratory braking using the UA, 3) expiratory braking using both PIIAdi and the UA, and 4) little expiratory braking with no PIIAdi. It appears that during periods of regular breathing, infants use PIIA early in expiration to oppose rapid emptying of the lungs, and that some degree of UA braking provides a variable, controlled resistance to airflow throughout expiration.

In the event of increased ventilatory demands, any significant braking could be reduced to provide a lower resistance leading to increased flow rates and $\dot{V}_{min}$. There is recent evidence that normal adults use their larynx in this manner. England and Bartlett (27) found that expiratory laryngeal braking is reduced during hyperpnea brought about by either CO_2 breathing or exercise in normal adults. It

is reasonable to assume that the newborn infant also uses the larynx to control expiratory airflow when challenged by chemical loads.

It has been shown in the preceeding chapter that the term neonate augments inspiratory airflow when challenged with a chemical load through the coordinated activation of pump and laryngeal muscles. Expiratory airflows are elevated as well, and the purpose of this investigation is to determine the extent to which changes in PIIAdi and PCA activity influence the expiratory pattern of the term neonate during CO₂ inhalation.

Experimental Design and Methods

Subjects and Measurements

Subjects consisted of 8 healthy term infants with demographics described in the preceeding chapter. The study protocol and measurements were also the same.

Data Analysis

Analytical techniques were similar to those in the preceeding paper. Values for PIIAdi were computed as the area under the diaphragm MTA above electrical zero from the onset of expiratory airflow until the MTA activity returned to within 1 SD of mean baseline activity. The time from the onset of expiratory airflow until the MTA returned to baseline is referred to as TPIIAdi, and this variable was used as another index of diaphragmatic braking (74). The mean and SD of PCA baseline (PCAb) activity was computed using 50 ms of MTA data around the point of minimum PCA activity during expiration.

Statistics were performed as in the preceeding paper with mean expiratory ($\bar{V}_e$), and peak expiratory ($pk\dot{V}_e$) flow rates, as well as V_t and $\dot{V}_{min}$ used as dependent variables for regressions. Electromyographic

data were used as independent variables. Additional regressions over time were performed within individuals in an effort to further describe the relationship between changes in muscle activities and changes in expiratory flow rates. A single expiration was divided into 10 equal time segments and average values for airflow, PCA activity and diaphragm activity were computed for each segment. This was done for each breath and mean values for these segment variables were computed for each 15-second period. Simple and multiple linear regressions were performed on each segment over time with flow as the dependent and PCA and diaphragm activities as the independent variables. Twenty sequential 15-second time periods were used for the regression beginning 1 minute before CO_2 breathing and ending after 4 minutes of CO_2 inhalation.

Ensemble flow/volume loops were created for each individual for the minute preceding CO_2 breathing and the fourth minute (steady-state) of CO_2 inhalation. The loops were computed by dividing individual inspired and expired volumes into 50 equal segments. These volumes and the corresponding flow rates were averaged for each segment, so that the composite loop consisted of 100 pairs of average points (50 inspired and 50 expired). Points were plotted with volume on the ordinate and flow on the abscissa to produce the composite figure.

Results

All 8 subjects reached 90% of the computed steady-state ventilatory response by the fourth CO_2 epoch. Times to reach 90% of steady-state are presented in Table 4-1. All subsequent comparisons of CO_2 to control values will refer to the fourth CO_2 epoch. The

individual and average data for changes in mechanical variables during CO_2 breathing are shown in Table 4-1. An average 42% increase in V_t with no timing change resulted in an average 38% increase in $\dot{V}_{\text{min}}$ that was highly correlated ($r=.94$, $P<0.001$) with the change in V_t . The augmentation of V_t with no change in timing resulted in significantly elevated $\bar{V}_e$ and $\text{pk}\dot{V}_e$ (Table 4-1). The flow rate changes were also highly correlated with increases in $\dot{V}_{\text{min}}$ ($r=0.95$ for $\text{pk}\dot{V}_e$, $r=0.97$ for $\bar{V}_e$, $P<0.0005$) since no change in T_e occurred.

A variety of breathing patterns were apparent during room-air breathing as described in the preceeding paper, but no matter what pattern an infant used breathing room air, the strategy remained basically unchanged with CO_2 breathing. This is apparent from an analysis of the overall shape of the composite flow-volume tracings from the individual subjects (Figure 4-1). Panels A-H of Figure 4-1 correspond to subjects 1-8, respectively. Six subjects adopted a pattern during room-air breathing (dotted curve) that included noticable braking using PIIAdi resulting in retardation of early expiratory airflow (Figure 4-1, panels B,C,D,E,F and H). This is seen as a steeper slope during early expiration (upper right quadrant of the flow-volume loop) indicating lower flow rates during the initial part of expiration. These subjects exhibited PIIAdi well into expiration ($\text{TPIIAdi}=0.34\pm0.09$ sec) which was maintained or prolonged during CO_2 breathing ($\text{TPIIAdi}=0.38\pm0.06$ sec). The other 2 subjects (Panels A and G) exhibited little diaphragmatic braking of expiration during both room-air and CO_2 breathing ($\text{TPIIAdi}=0.13\pm0.04$ and 0.13 ± 0.05 sec, respectively).

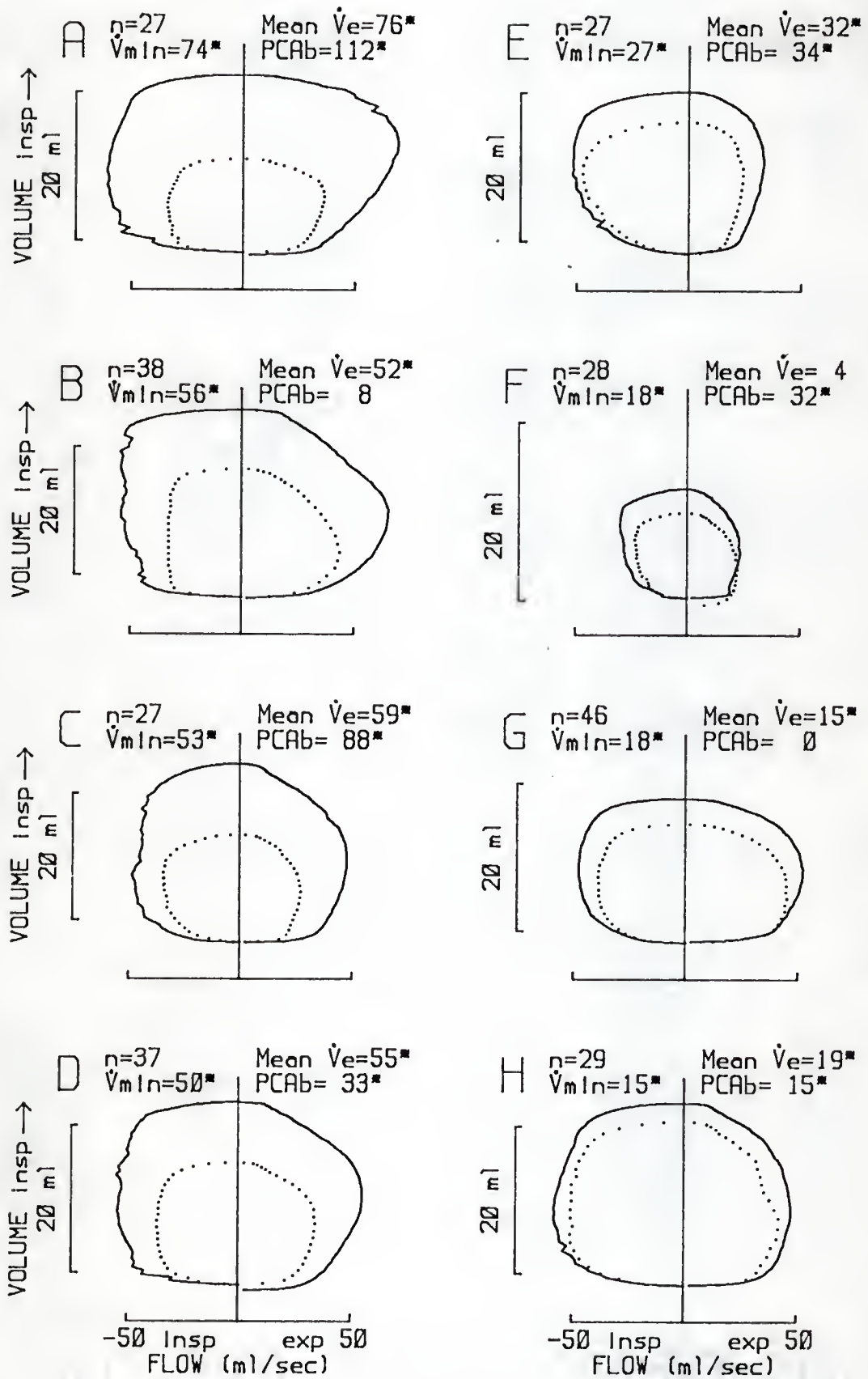
TABLE 4-1
Expiratory Electromyographic and Ventilatory Variables

Subject	$\dot{V}_{min}$	V_t	T_e	$\bar{V}_e$	$pk\dot{V}_e$	PCAb	PIIAdi	TPIIAdi
1	74*	91*	10	76*	87*	112*	-8	-12
2	56*	49*	-2	52*	51*	8	11	-6
3	53*	67*	5	59*	76*	88*	32	15
4	50*	49*	-1	55*	58*	33*	66*	24
5	27*	23*	-7	32*	36*	34*	-6	-9
6	18*	31*	17*	4	7	32*	73*	39*
7	18*	21*	5	15*	15*	0	7	9
8	15*	11	-6	19*	15	15*	21	31
$\bar{x} \pm SE$	38 $\pm$ 8*	42 $\pm$ 10*	3 $\pm$ 3	39 $\pm$ 9*	43 $\pm$ 11*	40 $\pm$ 15*	24 $\pm$ 12	11 $\pm$ 7
TTSS	98 $\pm$ 31	110 $\pm$ 35		98 $\pm$ 21	92 $\pm$ 25	154 $\pm$ 17		

Values are expressed as percent change from room-air breathing. Significant changes from room-air breathing ($P < 0.05$) indicated with "*".

FIGURE 4-1: Composite Flow-Volume Loops.

Panels A-H are data from subjects 1-8, respectively. Loops are composites for room-air --- and CO₂ — breathing. The number of breaths averaged for each subject is displayed (n), as well as the percent change in $\dot{V}_{min}$, $\dot{V}_e$, and PCAb. Significant changes are indicated with "*" (P<0.05).



To more thoroughly analyze the relationships between expiratory muscle activities and airflow, expiration was divided into 10 equal time segments and time-series regressions were performed as described in the methods. A summary of correlation coefficients is presented in Table 4-2. Data for diaphragm activity versus airflow are displayed for the first 2 segments, or 20% of mechanical expiration. Correlations between PCA activity and airflow are shown for the first 8 segments, or 80% of expiration. The first 2 segments will be collectively referred to as "early expiration", and the next 6 segments (20-80% of expiration) will be called "mid-expiration".

A positive correlation between diaphragm activity and early expiratory airflow was found in 3 subjects (Table 4-2, nos. 2, 4 and 8). These 3 subjects all had diaphragmatic braking, and all exhibited a positive correlation between PCA activity and airflow during early expiration. A negative correlation was observed between diaphragm activity and early expiratory airflow in 3 subjects (nos. 1, 3, and 6). Two of these 3 subjects had diaphragmatic braking (nos. 3 and 6) and no correlation between PCA activity and airflow during early expiration. Both subjects with little diaphragmatic braking (nos. 1 and 7) had a positive correlation between PCA activity and airflow during early expiration.

During all 6 mid-expiratory segments, 3 subjects (nos. 4, 6 and 8) exhibited a positive correlation between PCA activity and airflow. One subject (no. 5) had positive correlations in 5 of 6 segments, and 1 subject (no. 1) had positive correlations in 3 of 6 segments. All 5 subjects with positive correlations during mid-expiration had significantly increased PCAb (Table 4-1). The remaining subject with

TABLE 4-2
Correlation Coefficients Between Expiratory Flow Rates and
Muscle Activities

Subject	1	2	3	4	5	6	7	8
Diaphragm								
0-10%	-0.07	0.55*	-0.22	0.73*	0.04	-0.63*	0.25	0.42*
10-20%	-0.31	0.33	-0.39*	0.68*	-0.22	-0.44*	-0.27	0.47*
PCA								
0-10%	0.66*	0.61*	0.21	0.83*	0.02	0.06	0.45*	0.46*
10-20%	0.64*	0.56*	0.06	0.69*	-0.04	0.36	0.38*	0.53*
20-30%	0.58*	0.43*	-0.05	0.62*	0.30	0.60*	0.25	0.62*
30-40%	0.52*	0.26	-0.01	0.62*	0.47*	0.74*	0.02	0.73*
40-50%	0.38*	-0.10	0.07	0.70*	0.58*	0.84*	-0.16	0.85*
50-60%	0.33	-0.15	0.10	0.73*	0.79*	0.89*	-0.12	0.85*
60-70%	0.34	-0.20	0.19	0.74*	0.84*	0.89*	-0.35	0.81*
70-80%	0.34	-0.23	0.31	0.72*	0.82*	0.84*	-0.28	0.75*

Values are correlation coefficients between diaphragm and airflow for segments comprising the first 20% of expiration, and between PCA and airflow for segments comprising the first 80% of expiration for all 8 subjects. Regressions were performed on average values of these variables for 15-second time intervals beginning 1 minute before CO₂ inhalation and ending 4 minutes after the initiation of the challenge² (n=20 time intervals). Significant relationships (P<0.05) are marked with "*".

increased PCAb (no. 3) showed no significant correlation between PCA activity and airflow during mid-expiration. However, the combination of diaphragm and PCA activity in a multiple regression resulted in much higher regression coefficients for the first 5 mid-expiratory segments (20-70% of expiration, $r=0.79, 0.71, 0.65, 0.68$ and 0.54 , respectively) in this individual.

The changes in muscle activities during expiration with CO_2 breathing are summarized in Table 4-1. No significant change in PIIAdi with CO_2 inhalation was found, although there tended to be an increase ($24 \pm 12\%$, significant in 2 subjects). Individual regressions found PIIAdi correlated with $\bar{V}_e$ and $pk\dot{V}_e$ in only one subject ($r=-0.58$ and -0.55 , respectively). A slight overall increase in TPIIAdi was measured ($11 \pm 7\%$), but this was only significant in one subject. Values for TPIIAdi were correlated with $\bar{V}_e$ in 3 subjects ($r=-0.49 \pm 0.02$) and with $pk\dot{V}_e$ in 1 subject ($r=-0.49$).

An elevation of mean PCAb of $40 \pm 15\%$ was measured, with significant increases in six subjects. The changes in PCAb correlated with increases in $\bar{V}_e$ ($r=.70, P<0.05$) (Figure 4-2). Individual regressions found PCAb positively correlated with $\bar{V}_e$ in 4 subjects ($r=0.79 \pm 0.06$) and with $pk\dot{V}_e$ in 5 subjects ($r=0.77 \pm 0.11$). An example of an individual regression is shown in Figure 4-3.

Diaphragmatic braking parameters (PIIAdi and TPIIAdi) were combined with PCAb in a multiple regression in an attempt to better define changes in expiratory airflow. A significant multiple regression coefficient resulted in 5 subjects for both $\bar{V}_e$ and $pk\dot{V}_e$ ($r=0.82 \pm 0.11$ and 0.84 ± 0.09 , respectively) when all three parameters (PCAb, PIIAdi, TPIIAdi) were used as independent variables. Potential changes

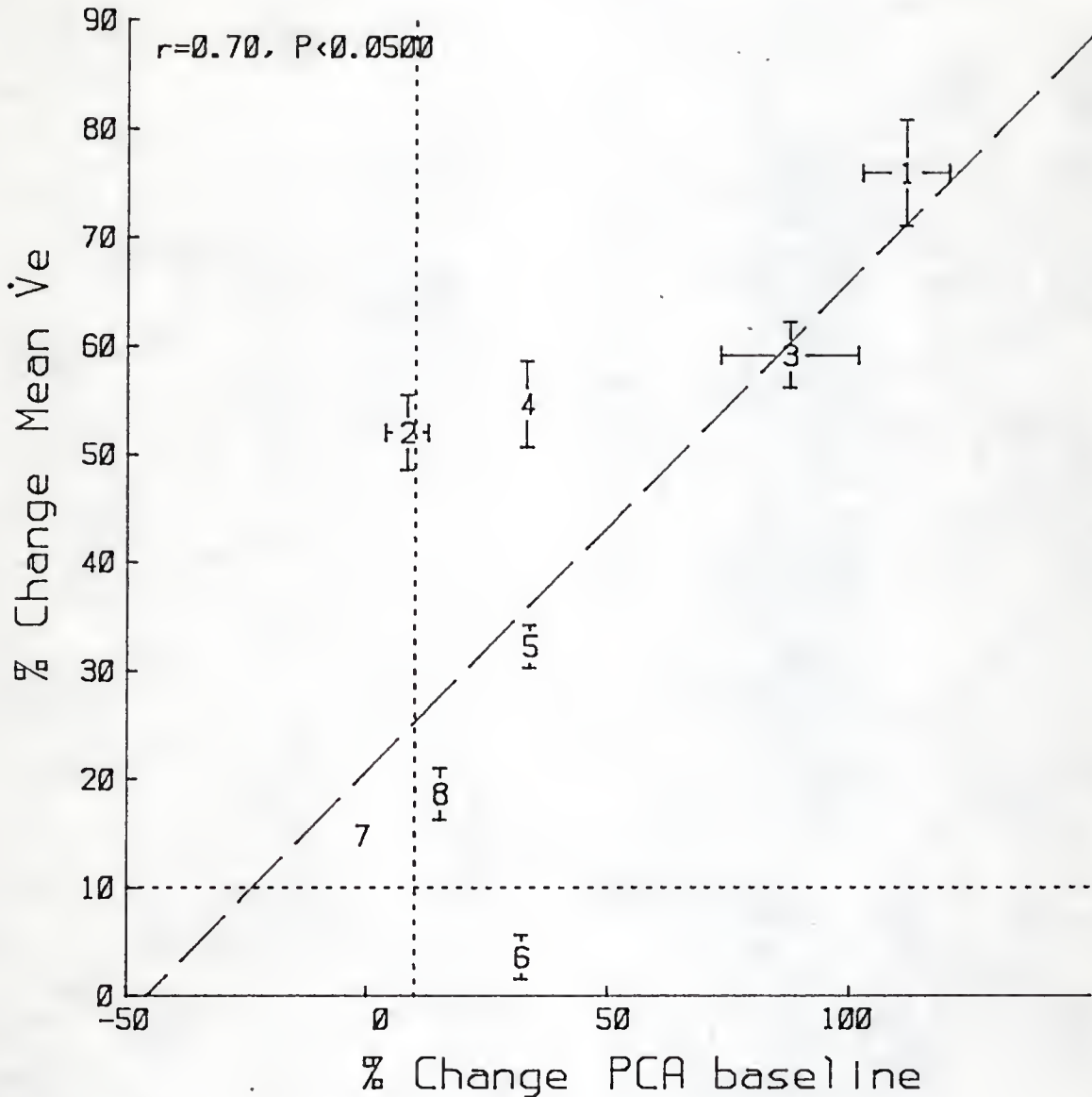


FIGURE 4-2: Expiratory Airflow versus PCA Muscle Activity.

Relationship between $\bar{V}_e$ and PCAb. Values are expressed as % change from room-air breathing. Points are mean $\pm$ SE for each of 8 subjects. A regression line is plotted (—) and the correlation coefficient (r) given. Points right of the vertical line (—) are significantly elevated PCAb ($P<0.05$). Points above the horizontal line (—) are significantly elevated $\bar{V}_e$ ($P<0.05$).

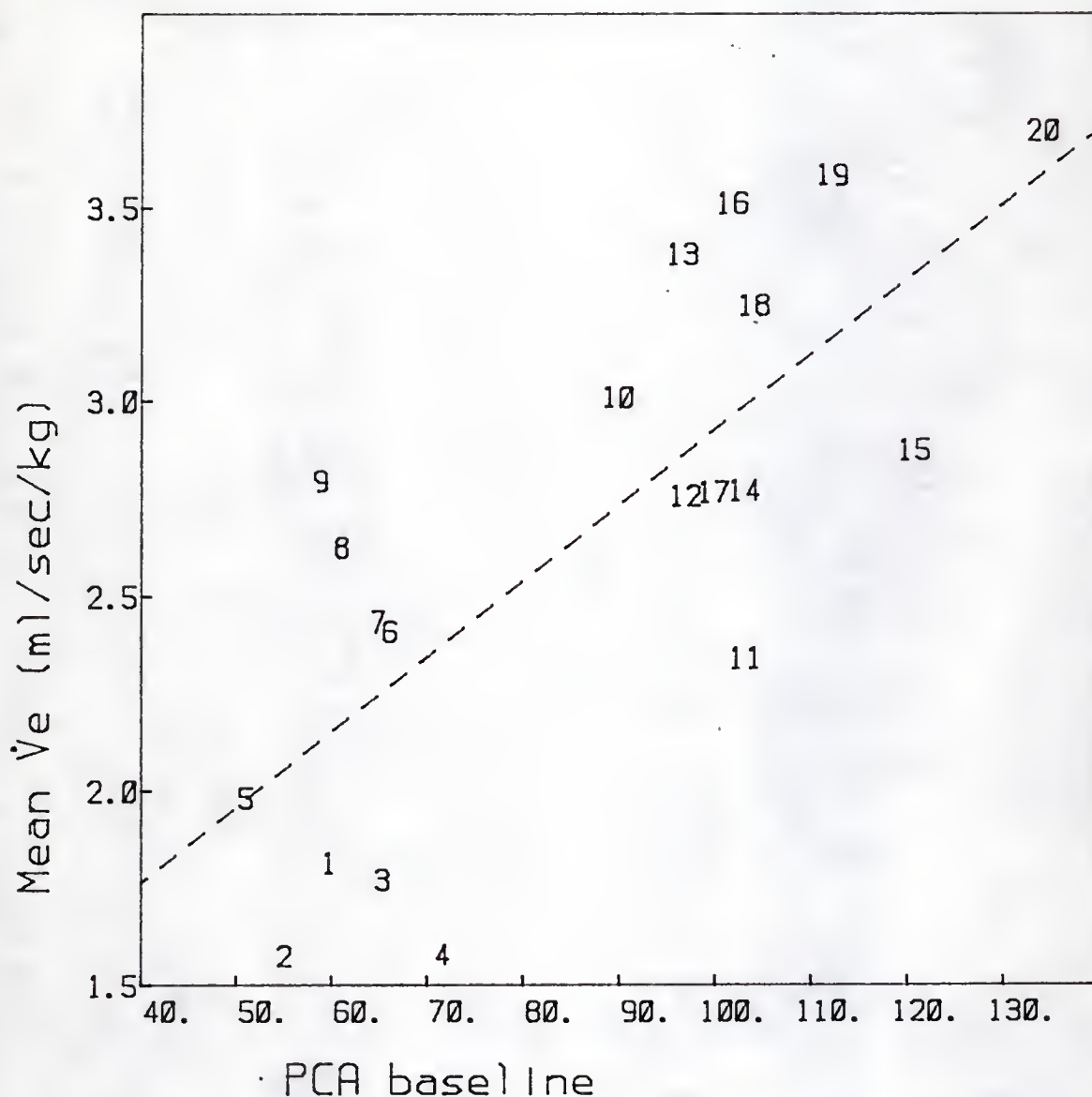


FIGURE 4-3: Example of an Individual Expiratory Regression.

Data are from Subject 8, showing the relationship between $\bar{V}_e$ and PCAb. Points are mean values for successive 15-second intervals starting 1 minute before CO_2 breathing and ending after 4 minutes of CO_2 breathing (20 points total). The correlation coefficient for this regression was 0.76 ($P < 0.0001$).

in lung recoil pressure were quantified by adding V_t to this regression. The resulting correlations with $\bar{V}_e$ and $pk\bar{V}_e$ were significant in all 8 subjects ($r=0.96 \pm 0.02$ for both).

Discussion

The healthy term infant in nonREM sleep augmented $\dot{V}_{min}$ during CO_2 breathing by increasing V_t with no change in frequency or timing as previously reported (2,22,25,45). An elevated V_t without timing changes requires increased inspiratory and expiratory flow rates. Three mechanisms by which expiratory airflow can be increased during hypercapnia are: 1) increased passive lung recoil pressure, 2) decreased expiratory braking, and 3) expiratory pump muscle activation. No respiratory activity from abdominal muscles was observed, and no change in expiratory activity of the intercostal muscles was found in any subject. Thus, one can conclude that the term infant does not use expiratory muscles when challenged with this level of CO_2 . The present study supports the idea that changes in lung recoil pressure combined with changes in UA braking are largely responsible for the observed increase in expiratory flow rates.

Individual breathing strategies must be examined in conjunction with passive mechanical changes influencing expiratory airflow. The increased V_t during CO_2 inhalation should increase passive lung recoil pressure unless EEV were lowered. No measure of EEV was made in the present study, and the flow-volume loops were normalized to EEV to better visualize changes in V_t and flow rates. There is no evidence to suggest that EEV is lowered, but a decay of expiratory flow at end-expiration which would suggest a lowering of EEV is not observed. It is, therefore, reasonable to assume lung

recoil pressure is elevated due to increased V_t . High correlations were observed between increased V_t and both $pk\dot{V}_e$ and $\bar{V}_e$ that were significant in all subjects ($r=0.88 \pm 0.09$ (SD) and 0.86 ± 0.08 , respectively). In a passive system, this would suggest that lung recoil pressure is a major contributing factor to changes in expiratory airflow. In the infant, with no observed expiratory muscle activity, increased lung recoil pressure is the driving force behind increased expiratory airflow. This passive mechanical influence on airflow acts in concert with changes in active expiratory braking mechanisms to shape the expiratory airflow pattern.

Changes in expiratory braking mechanisms with CO_2 breathing were observed. Expiratory braking is of particular importance to the neonate in maintaining an EEV above their low relaxation volume (63,71,72). One expiratory braking mechanism, PIIAdi, did not decrease during hypercapnia. In fact, it increased somewhat. This is contrary to findings in other animals (41,49,74), but consistent with the findings of Carlo et al. (16) in preterm infants and suggests that the elevation of EEV continues to be of vital importance in the newborn even during hypercapnia. The persistence of PIIAdi serves to retard early expiration and may partially counter the effect of increased passive recoil forces to augment $pk\dot{V}_e$. The data provide evidence that another mechanism, decreased laryngeal braking, is also involved in augmenting expiratory airflow.

The larynx serves as a variable resistor to control expiratory airflow in the spontaneously breathing infant (61) and adult human (12,28). Laryngeal braking of expiration can be accomplished through active laryngeal adduction (48), loss of active abduction (6,12) or a

combination of these factors (29). Conversely, decreased expiratory laryngeal resistance can result from decreased adductor activity and/or increased abductor tone (PCAb). Increases in PCAb coincident with decreased expiratory laryngeal resistance have been reported in both unanesthetized and anesthetized cats (4,6) and adult humans (13). Activities of other UA muscles have been shown to be related to changes in UA resistance in animals (29,48) and adult humans (96), but the larynx, acting as a flow valve, appears to be the primary UA region involved in the regulation of UA resistance (75). Unlike the PCA muscles, TA activity does not appear to play a role altering expiratory airflow in most adult animals (6,48) and humans (12). However, in newborn puppies (29) and lambs (48,51,54), TA activity is present during expiration, especially during quiet sleep.

It has been suggested that newborns use laryngeal adductors to brake expiratory airflow (36,61,71,80), however, it has not yet been possible to record adductor activity in infants. The present study indicates that elevated PCA activity correlates well ($r=0.70$) with, but does not fully explain, changes in $\bar{V}_E$ during hypercapnia. However, a combination of changes in V_t (lung recoil pressure), PCAb and diaphragm braking consistently correlate highly with $\bar{V}_E$ ($r>0.94$ in each subject). This high correlation leaves little to add to the description of expiratory flow rates, suggesting that either laryngeal adductor activity is of little importance in the response of the newborn to CO_2 , or that the adductors act conversely to the abductors in a highly synchronized fashion. The reciprocal activation of these muscles was evident in previous studies in newborn puppies (29) and indicates a high degree of intercorellation between the activities of

the laryngeal adductors and abductors. Therefore, if it was possible, the addition of adductor activity to the present description of expiratory flow rates would likely be insignificant whether or not the muscles were actively contributing to the response. However, one cannot exclude the possibility of laryngeal adductors playing a role in shaping expiratory airflow and the reciprocal activation of these muscles may be necessary to bring about any appreciable change in laryngeal caliber.

In the preceeding chapter it was found that a variety of breathing strategies may be invoked to augment inspiratory airflow. The same can also be said for expiratory airflow. Three basic relationships were observed between muscle activities and expiratory airflow. These are: 1) positive correlations of both PIIAdi and PCA with early expiratory airflow, 2) negative correlations between PIIAdi and early expiratory airflow with no relationship to PCA activity, and 3) good correlations between PCA and expiratory airflow during early and/or mid-expiration along with little PIIAdi.

A positive correlation between PIIAdi and early expiratory airflow indicates that augmented PIIAdi coincided with increased airflow. This could only be possible if another mechanism was involved to counter the effect of increased diaphragmatic braking. Three of the subjects with substantial PIIAdi while breathing both room air and CO₂ (nos. 2,4 and 8) had positive correlations between diaphragm activity and airflow during early expiration. These 3 subjects also had significant correlations between PCA activity and airflow during the same time period. This suggests that increased diaphragm activity is coupled with increased PCA activation in these subjects, and that any

retardation of $\dot{p}_{\dot{V}_E}$ that may have been afforded by PIIAdi is offset by increased PCA activity.

One would suspect that those subjects that relied on PIIAdi to brake early expiration (nos. 2,3,4,5,6 and 8) might have good negative correlations between diaphragm activity and early expiratory airflow, such that reduced PIIAdi would coincide with increased expiratory airflow. In fact, only 2 of 6 subjects with substantial PIIAdi exhibited such a relationship. Those 2 subjects (nos. 3 and 6) showed little correlation between PCA activity and airflow in early expiration. Without an early increase in PCA activity, braking of expiratory airflow by the diaphragm goes unopposed.

Subject 6 exhibited the largest increase in diaphragmatic braking with CO_2 breathing and this resulted in no change in $\dot{p}_{\dot{V}_E}$ (Table 4-1). This suggests that increased PIIAdi fully compensated for any increased recoil pressure due to elevated V_t . An elevation of PCAb was also observed in this subject (Table 4-1), and this is reflected in good correlations between PCA activity and flow rates during mid-expiration (Table 4-2). This expiratory PCA activity may reflect an effort to shorten T_e in the face of augmented diaphragmatic braking (39% increase in T_{PIIAdi}). In fact, T_e was prolonged 17% in this subject, but increased $\dot{V}_{\text{min}}$ was still achieved through elevated V_t .

The other subject that exhibited a negative diaphragm-airflow correlation in early expiration (no. 3), used a combination of increased pump muscle and PCA activity to augment inspiratory airflow (Table 3-2). This subject also appears to use a combination of diaphragm and PCA muscles to modulate expiratory airflow. The negative correlations between diaphragm or PCA activity and airflow during

early expiration and mid-expiration were unimpressive (Table 4-2), however, a multiple regression using both muscle activities to describe airflow resulted in significant contributions of both muscles to correlation coefficients that averaged 0.71 for the first 6 expiratory time segments. This suggests that activities of the diaphragm and PCA muscles alone cannot explain much of the variability in expiratory airflow in this subject, but the coordinated action of these muscles together can explain 50% ($r^2=0.50$) of the observed variability in airflow.

Both subjects (nos. 1 and 7) that established a relatively unbraked ventilatory pattern during both room-air and CO₂ breathing, exhibited significant correlations between PCA activity and airflow during early and, for subject 1, mid-expiration. In addition, both of these subjects showed no increase in diaphragm activity during inspiration (Table 3-2) suggesting that laryngeal modulation of airflow throughout the respiratory cycle was the dominant factor in the hypercapnic response of these individuals.

In spite of the variations in breathing strategy between individuals, the expiratory flow-volume patterns of individual subjects varied little between room-air and CO₂ breathing (Figure 4-1). The predominant pattern exhibited a retardation of early expiratory airflow related to PIIAdi, but no matter what strategy was adopted to maintain EEV, no appreciable change in strategy occurred within the time course of these experiments. This suggests that preserving an expiratory pattern to defend EEV is critical and is maintained in spite of changes associated with this level of CO₂ inhalation.

In summary, the response of the newborn to CO_2 inhalation depends on the coordinated activation of the diaphragm and laryngeal muscles to bring about increased expiratory airflow with little change in timing. The relative contributions of these muscles to individual subject's ventilatory responses varied greatly, yet resulted in a common outcome of increased V_t and $\dot{V}_{\text{min}}$ with little change in respiratory cycle timing. The most frequently observed breathing strategy involved maintained PIIAdi and increased PCAb, with PCA activity consistently exhibiting higher correlations than the diaphragm with changes in expiratory flow rates. The persistent PIIAdi may serve to offset changes in lung recoil pressure and appears to be more tightly coupled to the maintenance of EEV, while other airflow-controlling muscles of the UA appear active in modulating resistance to airflow to help bring about the V_t changes necessary to increase $\dot{V}_{\text{min}}$ during CO_2 breathing.

CHAPTER 5

MECHANISMS CONTROLLING INSPIRATORY AND EXPIRATORY DURATION

The newborn infant responds to low levels of CO_2 inhalation by elevating $\dot{V}_{\text{min}}$ through increased V_t with little change in T_i , T_e or frequency of breathing. This is achieved by augmenting PCA muscle activity throughout the respiratory cycle and by increasing inspiratory pump muscle activity. Augmentation of inspPCA and inspIC exceeded that of inspDI and correlated well with inspiratory flow rates. Changes in expiratory braking consisted of minimal modulation of PIIAdi and increased PCAb reflecting a decrease in laryngeal braking. Thus far, inspiration and expiration have been treated separately, yet to fully appreciate the responses of the individuals a discussion of the total response is necessary.

The use of EMGs as an estimate of neuromuscular response has potential problems. Poor electrode placement, deterioration of electrode contact and, especially with the laryngeal electrode, movement of the electrode can all contribute to erroneous measurements. Good electrode placement was confirmed by the measurement of phasic inspiratory activity of the muscles in question. Studies did not last more than 2 hours, and in this time period no deterioration of the EMG was observed. The prevention of faulty measurements due to movement was achieved by analyzing only those experiments where the subject did not move or swallow throughout the recording period.

Another complicating factor in using EMGs to describe mechanical changes is that the relationship between muscle activation and mechanical changes is most likely alinear. The amount of force generated for a given increase in EMG measured would depend on several factors, including the resting length of the muscle itself. Additionally, resistance to airflow is related to the inverse of the radius of the tube to the fourth power. Even if the relationship between PCA muscle activation and laryngeal caliber is linear, airflow resistance would not be linearly related to the PCA EMG changes. Thus, any correlations between the measured changes in EMG activity and changes in mechanical variables like airflow and V_t are first approximations, at best.

There appears to be an order to the recruitment pattern of the various muscles with the exception of only one subject (no. 2). All subjects that increased inspDI also increased inspIC . Likewise, excluding subject 2, those subjects that increased inspIC elevated inspPCA . Those subjects that augmented PCAb also increased inspPCA , and the two subjects with increased PTIAdi exhibited elevated PCAb . This suggests that the general response of the newborn is to increase primarily PCA muscle activity during both inspiration and expiration. Secondly, pump muscle augmentation can contribute to the hypercapneic response in the form of intercostal muscle recruitment to stiffen the chestwall and allow the diaphragm to pump more effectively. This increased mechanical efficiency of the diaphragm may account for the smaller augmentation of inspDI observed. Lastly, the diaphragm itself can be recruited to elevate inspiratory flow rates.

The relationship between increases in inspPCA and PCAb is significant, as shown in Figure 5-1. The correlation coefficient of 0.94 means that 88% ($r^2=0.88$) of the variability in PCAb is reflected in changes in inspPCA. This implies that all of the subjects modulated inspPCA and PCAb to the same relative degree. Bartlett (4) found that with hyperoxic CO_2 breathing, both inspiratory and expiratory laryngeal resistance fell in conjunction with increased PCA activity in anesthetized cats. When changes in inspiratory and expiratory resistance from Bartlett's (4) individual animals are plotted against each other (Figure 5-2) a linear relationship is found with $r=0.7$ ($P<0.05$). This relationship is markedly improved when, what appears to be an outlier (no.5), is removed. The correlation coefficient then becomes 0.93 ($P<0.001$), almost identical to the correlation in PCA activities found in the present study (Figure 5-1).

The relationship between T_i and T_{PIIAdi} is also of importance. A study on anesthetized dogs (74) breathing 100% oxygen found that those animals with little $PIIAdi$ ($T_{PIIAdi}<0.24$ sec.) had significantly shorter inspiratory times than those animals with $T_{PIIAdi}>0.32$ seconds ($T_i=0.51\pm0.07$ (mean $\pm$ SE) and 0.92 ± 0.13 , respectively, $P<0.01$). When the present data are plotted in this manner, a similar relationship is seen (Figure 5-3). The correlations, slopes and intercepts are similar between room-air and CO_2 breathing (Table 5-1), hence, all data were combined in a regression resulting in a correlation between T_i and T_{PIIAdi} ($r=0.67$, $P<0.005$). In the study on dogs (74) this relationship was maintained during hyperoxic CO_2 rebreathing with both T_i and T_{PIIAdi} shortening in those animals that had substantial diaphragmatic braking initially. Those animals with

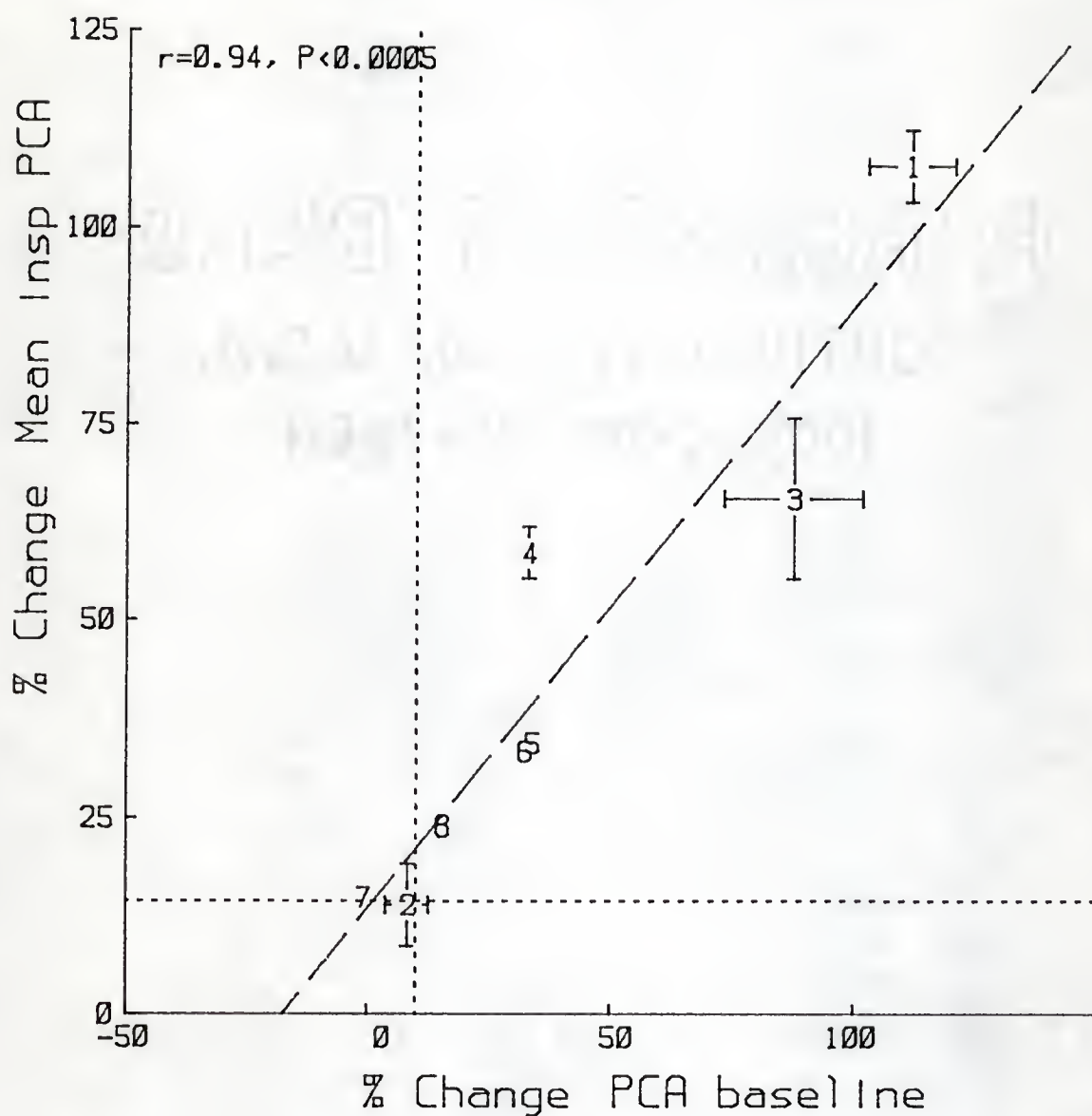


FIGURE 5-1: Inspiratory versus Expiratory PCA Muscle Activity.

Values are expressed as % change from room-air breathing. Points are mean $\pm$ SE for each of 8 subjects. A regression line is plotted (— — —) and the correlation coefficient (r) given. Points right of the vertical line (—) are significantly elevated PCA_b ($P<0.05$). Points above the horizontal line (—) are significantly elevated inspPCA ($P<0.05$).

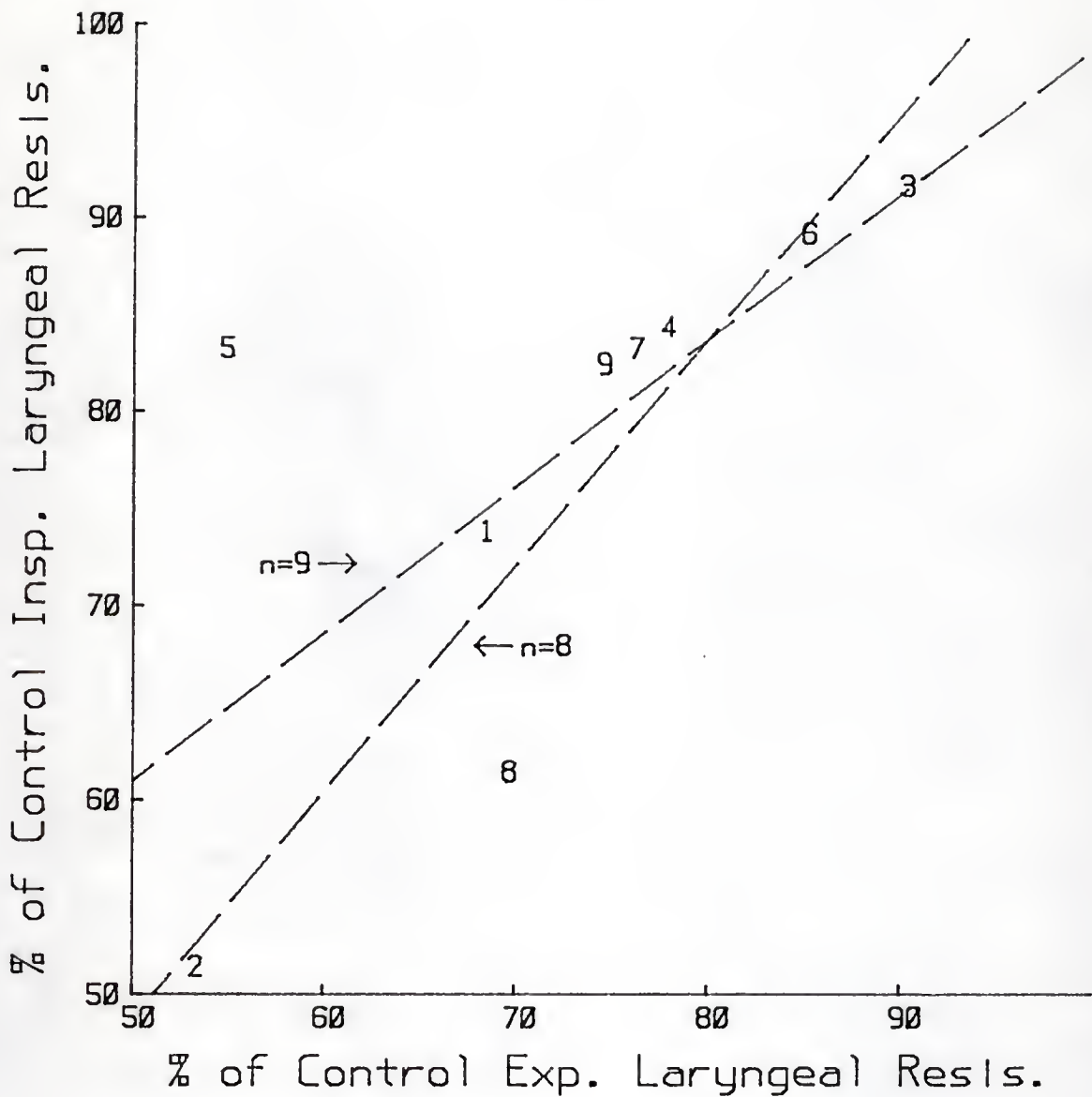


FIGURE 5-2: Laryngeal Resistance in Cats.

Data from Bartlett (4) from anesthetized cats breathing CO_2 . Plotted as percent of control expiratory resistance versus percent² of control inspiratory laryngeal resistance. A regression line (— — —) is plotted for both 9 and 8 (no. 5 excluded) subjects.

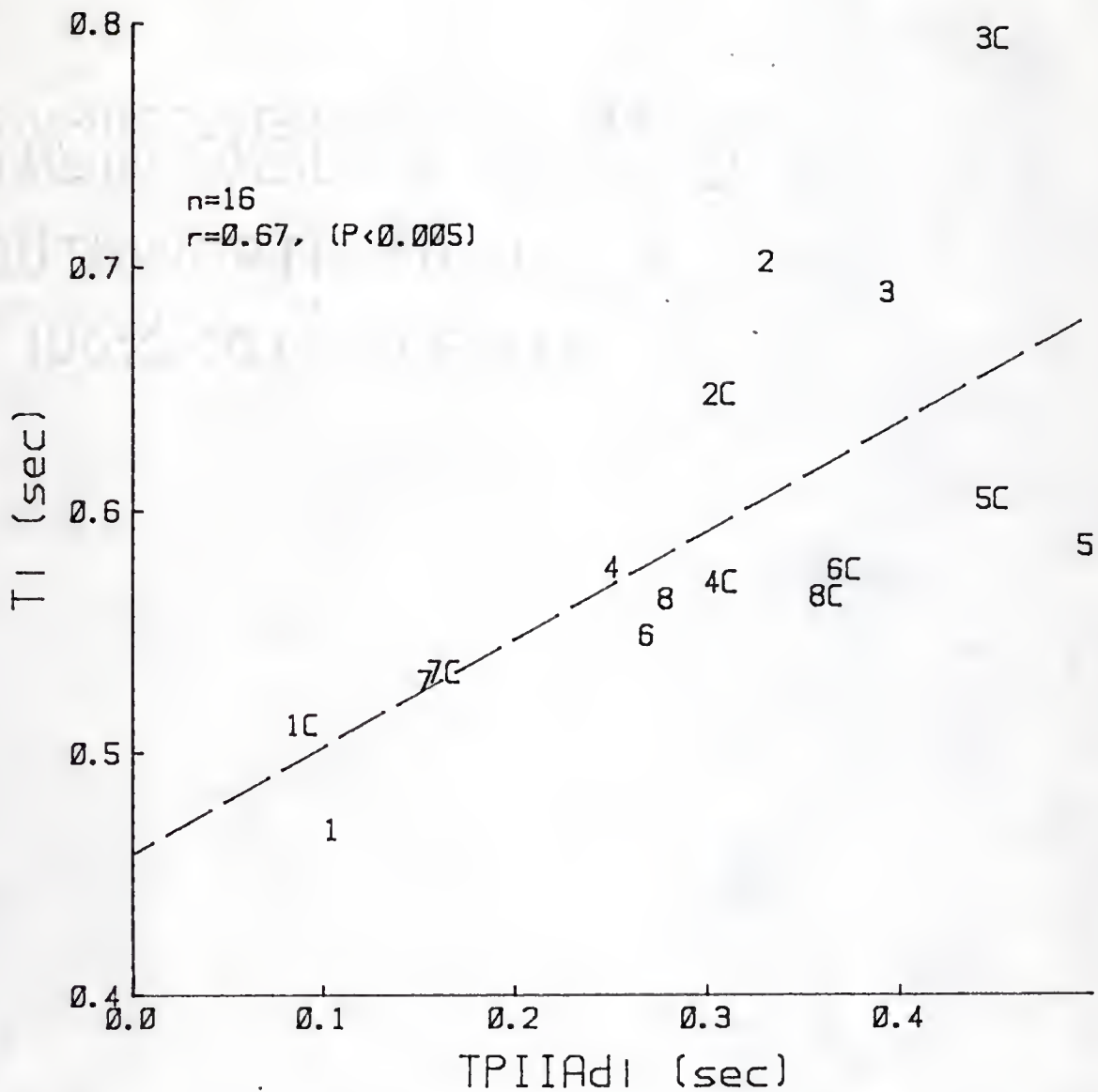


FIGURE 5-3: Inspiratory Time versus Diaphragmatic Braking.

Subject numbers are displayed for values during room-air and CO_2 (C) breathing. A regression line (— — —) is plotted for all data ($n=16$).

TABLE 5-1
Regressions Using TPIIAdi

	n	Correlation Coefficient	Slope	Intercept
Ti vs. TPIIAdi, room air	8	0.67	0.42	0.46
CO ₂	8	0.67	0.46	0.45
combined	16	0.67	0.44	0.46
Te vs. TPIIAdi, room air	8	0.95	1.43	0.30
CO ₂	8	0.96	1.13	0.37
combined	16	0.95	1.27	0.33

little PIIAdi during O_2 breathing showed no change in Ti or TPIIAdi with CO_2 rebreathing. Vagotomy abolished the shortening of TPIIAdi and Ti during rebreathing suggesting a vagal modulation of PIIAdi and Ti.

The action of the diaphragm to brake expiration suggests that a similar relationship between TPIIAdi and Te may exist, where Te is prolonged by increased TPIIAdi. Oliven et al. (74) found that there was no relation between Te and TPIIAdi in anesthetized dogs, but their subjects were using expiratory muscles to actively expire which may have profound effects on Te. In the present study, such a relationship exists between Te and TPIIAdi (Figure 5-4). Correlations, slopes and intercepts were similar between room-air and CO_2 breathing (Table 5-1), and again all data were combined in a regression resulting in a high correlation ($r=0.95$, $P<0.0001$). The correlation coefficient was much higher than for Ti and TPIIAdi suggesting a tighter linkage between TPIIA and the control of expiratory duration. This further suggests that the newborn actively controls Te using diaphragmatic braking. However, when individual changes in Te and TPIIAdi are considered, subjects 1,4 and 8 exhibit Te/TPIIAdi relationships with negative slopes (Figure 5-4), contrary to the overall response. The tight coupling between diaphragmatic braking and Te, and, thus EEV, observed in Figure 5-4 suggests that the overall strategy of breathing and the pattern of respiratory cycle timing that an infant adopts is related to the level of diaphragmatic braking. However, the individual responses to CO_2 breathing depend primarily on modulation of expiratory airflow resistance through another mechanism; active laryngeal dilation.

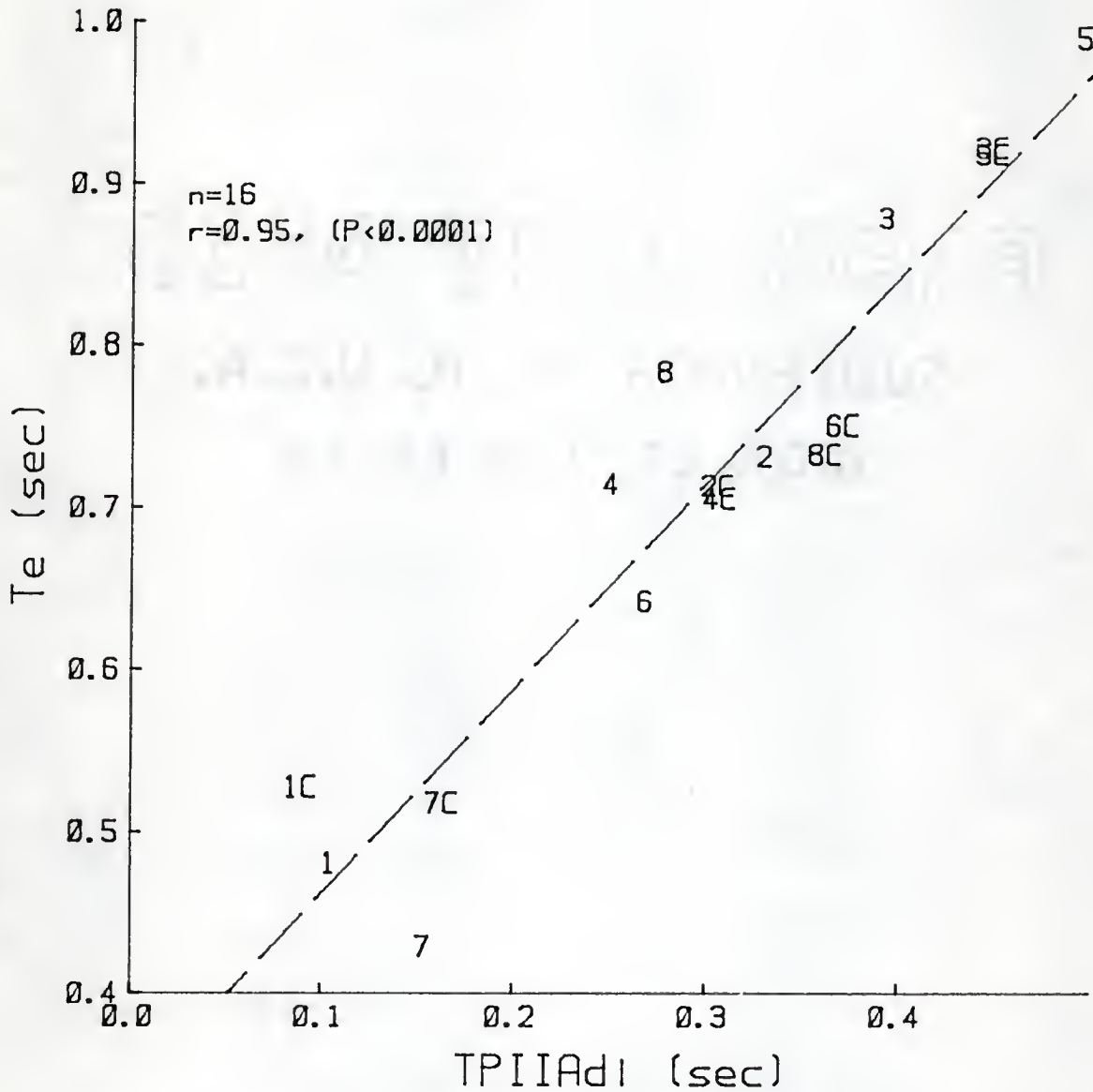


FIGURE 5-4: Expiratory Time versus Diaphragmatic Braking.

Subject numbers are displayed for values during room-air and CO_2 (C) breathing. A regression line (— — —) is plotted for all data ($n=16$).

The Inspiratory Off-Switch

The reflex mechanisms responsible for the observed increases in inspiratory muscle activation and expiratory laryngeal dilation with CO_2 inhalation are unknown. It is speculated that the neonatal respiratory control system is similar to that described in experimental animals. The results of this study will be related to the inspiratory off-switch model. Several studies have attempted to model the central pattern generator (CPG) for rhythmic respiration. Studies to localize various respiratory neuronal pools have utilized several techniques in experimental animals including transections, electrical stimulation and intracellular recording of respiratory related neuronal activity. Further studies have been performed to describe the interactions between neuronal groups as well as the reflex responses of these cells to a variety of stimuli. Numerous models have been proposed to integrate these studies into a functional description of the CPG and its reflex responses. Most descriptions of the CPG divide the respiratory cycle into four phases (30): 1) inspiratory phase with augmented inspiratory activity, 2) inspiratory off-switch phase, 3) expiratory phase 1 with PIIA, and 4) expiratory phase 2 with increased inspiratory inhibition and augmented expiratory motor activity with increased drive. The inspiratory off-switch controls the amplitude and duration of a central inspiratory activity (CIA) integrator while this integrator is kept inhibited during expiration by mechanisms controlling PIIA and expiratory muscle recruitment thresholds. No expiratory pump muscle activity was observed in these infants, so the final phase including expiratory motor activity will not be addressed.

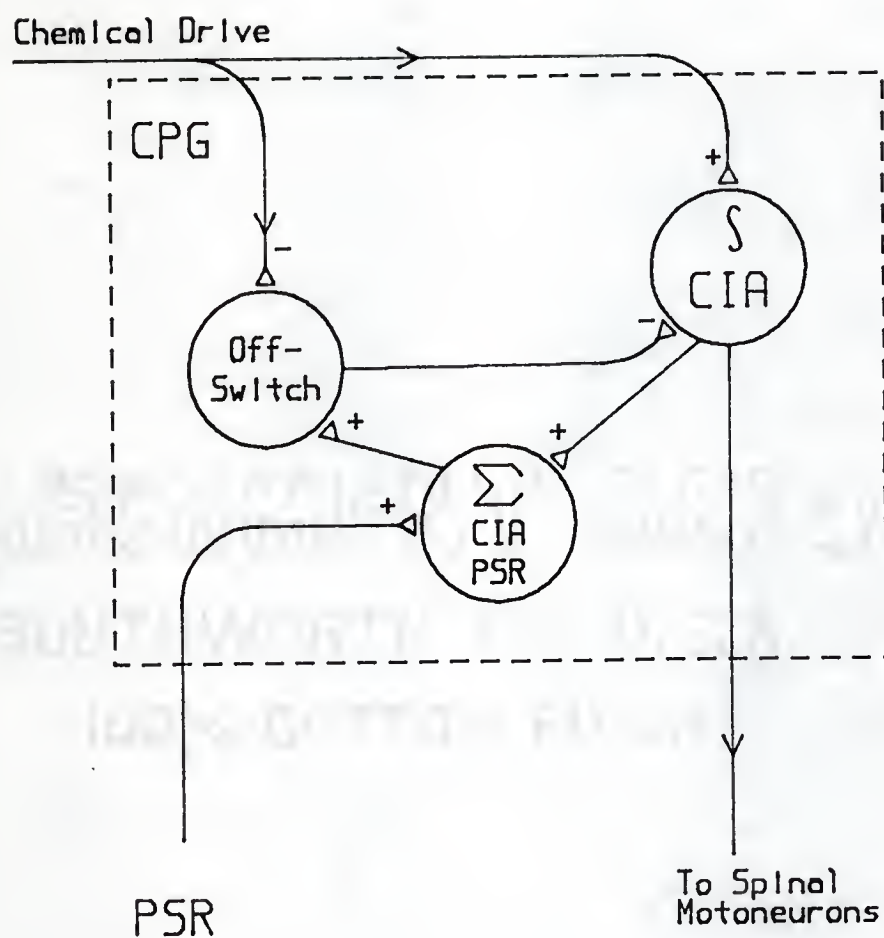


FIGURE 5-5: Model of Inspiratory Off-Switch.

A hypothetical model adapted from Bradley et al. (11) depicting one version of the off-switch mechanism of the CPG. Inhibitory (-) and excitatory (+) connections are noted.

A general model describing the functional organization of the inspiratory off-switch mechanism of the CPG is shown in Figure 5-5. The amplitude and duration of inspiration are determined by the integration of negative influences from the off-switch and stimulation from chemical and other drives. The output from the off-switch is augmented by a combination of feedback from the CIA and lung volume related pulmonary stretch receptor (PSR) activity and is inhibited by chemical and other drives. The relationship between amplitude and timing of inspiration, or V_t - T_i has been extensively studied in numerous species. The Hering-Breuer inspiratory-inhibitory inflation reflex (14) describes a PSR-mediated termination of inspiration. The volume threshold for the reflex termination of inspiration has been found to fall rapidly during the course of inspiration in most animals (19,34,44) and infants (60). The V_t - T_i relationship depicting a declining volume threshold for termination of inspiration is shown in Figure 5-6.

Stimulation of respiration through CO_2 breathing causes increased rate of rise of phrenic nerve activity in the lightly anesthetized cat (19). This increased rate of rise would result in a shortening of T_i , as seen with increased temperature in cats (30), unless the off-switch threshold is raised. The latter appears to be the case in cats (19) with an elevation of the off-switch threshold allowing a larger V_t . In the present study, the increase in V_t was accompanied by no change in T_i . This suggests that in the term infant, the inhibitory effects of CO_2 on the off-switch (raising the off-switch threshold) balance the increased excitatory feedback from the CIA and PSRs that would act to shorten T_i . There are two ways to

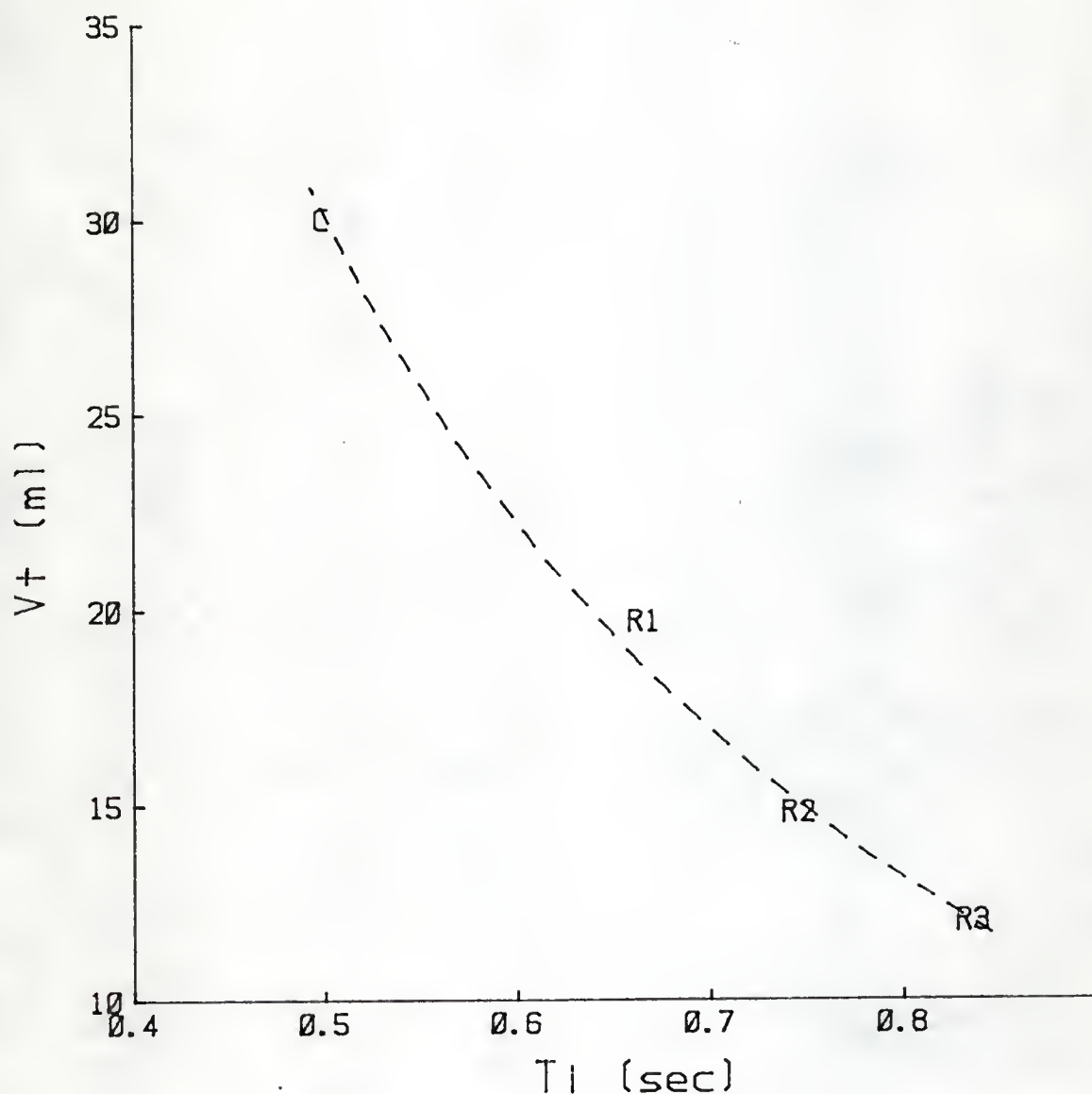


FIGURE 5-6: Declining Inspiratory Off-Switch Threshold.

Plot of V_t versus T_i adapted from Kosch et al. (60). Data is from term infants during control breathing (C) and three levels of single-breath inspiratory resistive loading (R1,R2,R3).

interpret these results; either there is a range of the V_t - T_i relationship where V_t continues to increase without a shortening of T_i , or the increased V_t is due to a shift of the entire V_t - T_i curve to the right as shown in Figure 5-7. Additionally, these data provide evidence of a variable amplitude effect of CO_2 on the neuronal pools mediating the activity of the diaphragm, intercostal and PCA muscles.

Inspiratory-Expiratory Coupling

The expiratory phase of respiration is generally thought of as a passive mechanical event during eupneic breathing, with a decay of volume being brought about by elastic recoil of the lungs. In fact, the control of expiratory duration is far from passive. There are neuronal pools that discharge in a declining manner in early expiration in close correspondence with PIIA (82,83). This PIIA counters elastic recoil and slows emptying of the lung and is coupled to a prolongation of T_e as described earlier (Figure 5-4). This PIIA is an efficient means of braking expiration, for it is achieved by the negative work of activating the diaphragmatic muscle fibers while they are stretching. This stretching contraction retards expiratory airflow at a low energy cost to the infant. The prolongation of T_e through the retardation of volume decay is hypothesized to be mediated by the feedback of PSR activity on a neuronal pool that integrates factors controlling central inspiratory-inhibition (CII) (56,57,104). Factors that serve to slow the emptying of the lungs, including PIIA and increased UA resistance, reflexly prolong expiration. These influences on CII are integrated into a more comprehensive model of respiratory control in Figure 5-8.

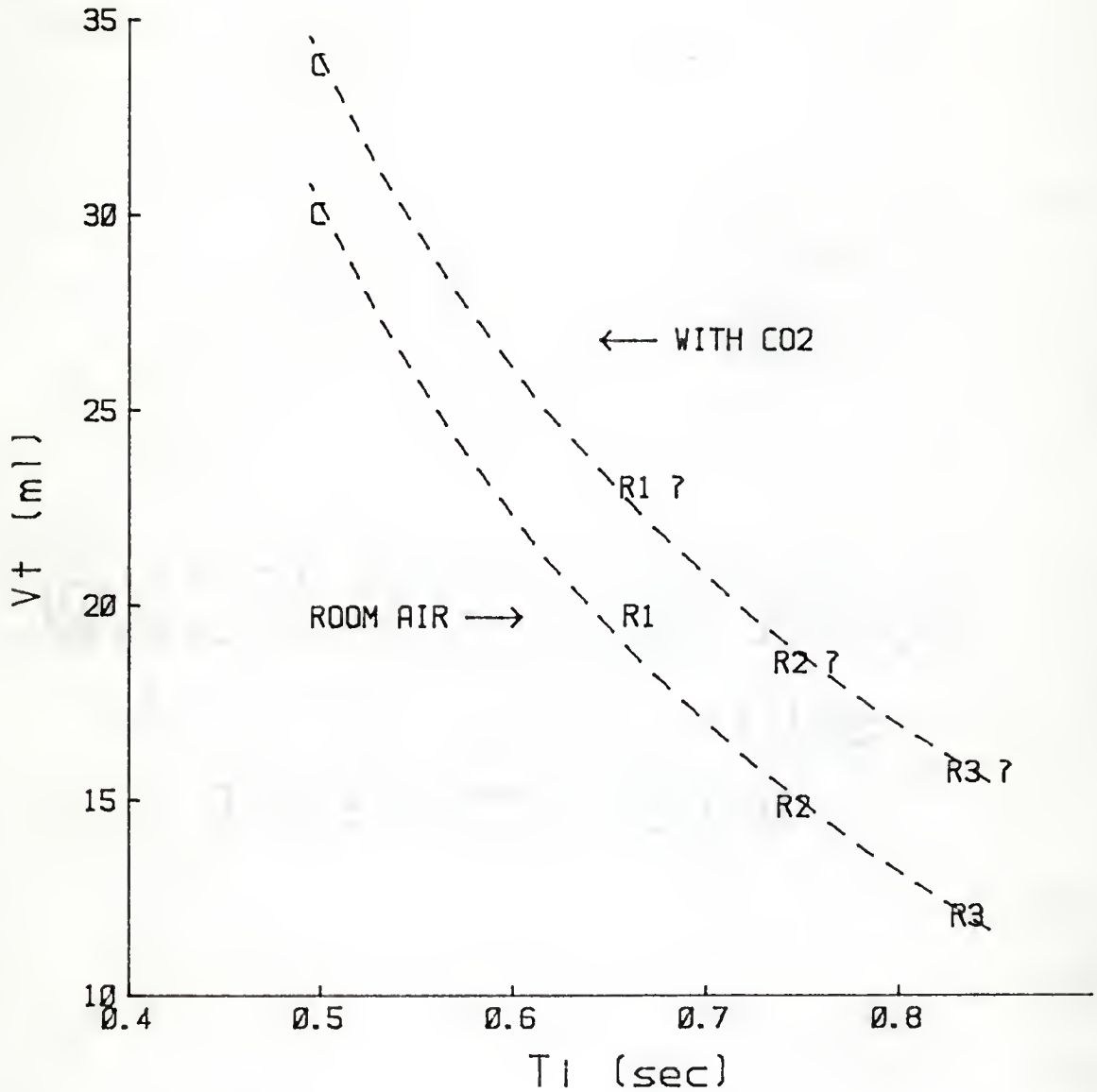


FIGURE 5-7: Effect of CO₂ on Vt-Ti Curve.

Hypothetical effect of CO₂ breathing on the declining inspiratory off-switch threshold in infants. Room-air breathing curve adapted from Kosch et al. (60). A "?" indicates unknown data.

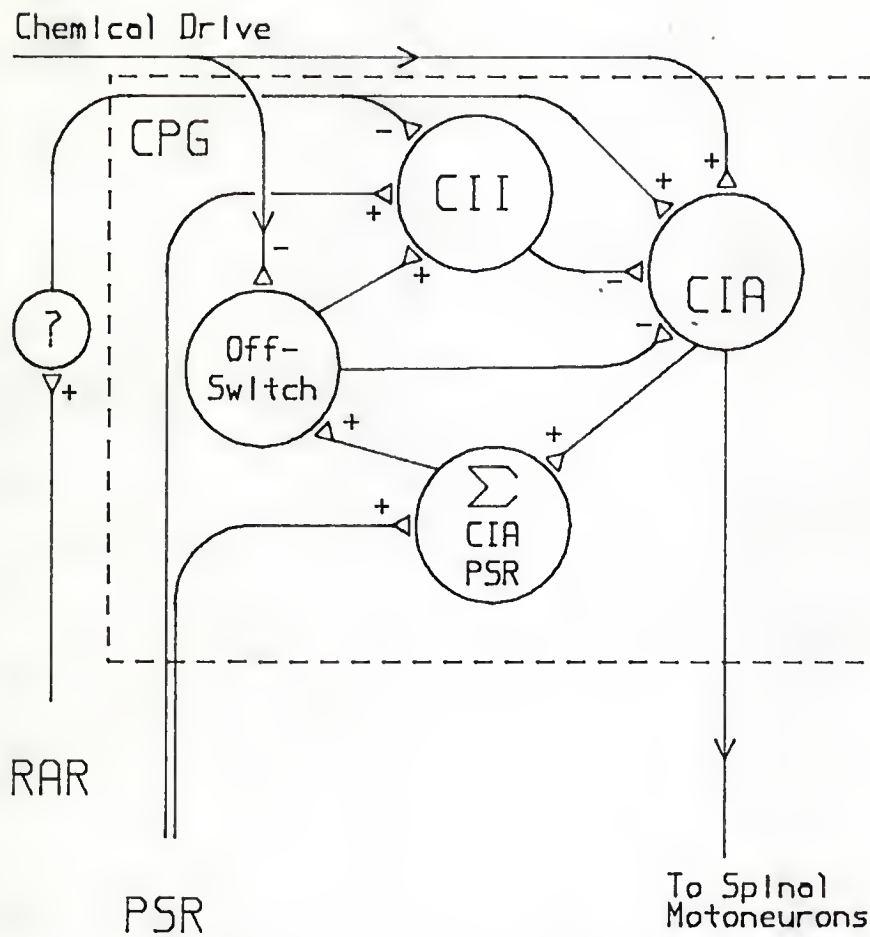


FIGURE 5-8: Model of Central Inspiratory Inhibition.

Model adapted from Knox (57) depicting the interaction of a central inspiratory inhibitory neuronal pool controlling T_e with the off-switch model from Figure 5-5.

The CII neuronal pool has been added to this model and the output from these neurons has an inhibitory effect on CIA. CII neurons are shown to be excited by PSR feedback as well as by off-switch output in this model. An additional input to the CPG, rapidly adapting receptor (RAR) feedback, is introduced in this model. These receptors are generally thought to respond to high flow rates and low lung volumes (30,57). They are shown as having an inspiratory excitatory effect on the CIA and a corresponding inhibitory input to the CII neurons.

The manner in which PIIA neurons and neurons controlling laryngeal aperture fit into this model is largely unknown. Some information does exist on the vagal modulation of PIIA and laryngeal caliber or muscle activity, as well as the effects of increased respiratory drive on these potential expiratory braking mechanisms. This information, combined with results from the present studies, allow one to speculate on the relationship of the neurons controlling these functions with the CPG.

A reduction in vagal afferent input results in decreased PIIA in the lamb (51), suggesting that breathing at higher lung volumes augments PIIA. Studies on anesthetized (74) and awake (93) dogs breathing various CO_2 gas mixtures found a decrease in PIIAdi along with decreasing T_e . A study on premature infants reported no change in PIIAdi with CO_2 breathing (16), with no mention of changes in respiratory cycle timing. The lack of PIIA modulation with CO_2 in the premature infants is contrary to the findings in animals, however there is also no change in T_e in the studies on premature infants as measured from the tracings of raw data. These data, in combination

with the present studies, suggest that the relationship between T_e and $PIIAdi$ in the infant is unchanged by CO_2 breathing.

The effect of lung inflation on laryngeal caliber or PCA activity is complex and variable. Investigators have reported augmentation of PCA activity or laryngeal widening with lung inflation (6,23,68) while others have observed or inferred reflex adduction of the vocal cords with this stimulus (31,38). Reflex increases in laryngeal abduction or abductor muscle activity with CO_2 breathing are well defined in the literature. Increases in PCA activity or laryngeal caliber have been observed with CO_2 breathing during both inspiration and expiration in cats (4,6), adult humans (27), and premature infants (18). This information, combined with the present data, indicates a clear augmentation of laryngeal abductor activity with CO_2 breathing. Modulation of laryngeal caliber by PSR feedback mechanisms cannot be explicitly described from the current body of knowledge.

Proposed Model of Respiratory Control in the Newborn

A model is proposed in Figure 5-9 that incorporates $PIIA$ and PCA controllers, as well as the motoneuron pools of the diaphragm, intercostal and PCA muscles. This model shows diaphragm and intercostal muscles acting synergistically to drive the respiratory pump. Activation of the PCA muscles is shown to decrease laryngeal resistance to airflow which combines with inspiratory drive to increase lung volume. Changes in lung volume, in turn, modulate PSR feedback to the CPG.

The $PIIA$ neurons are most likely no different from the phrenic motoneurons. The observation of $PIIA$ probably reflects a lowering of the inhibitory influences on the CIA during early

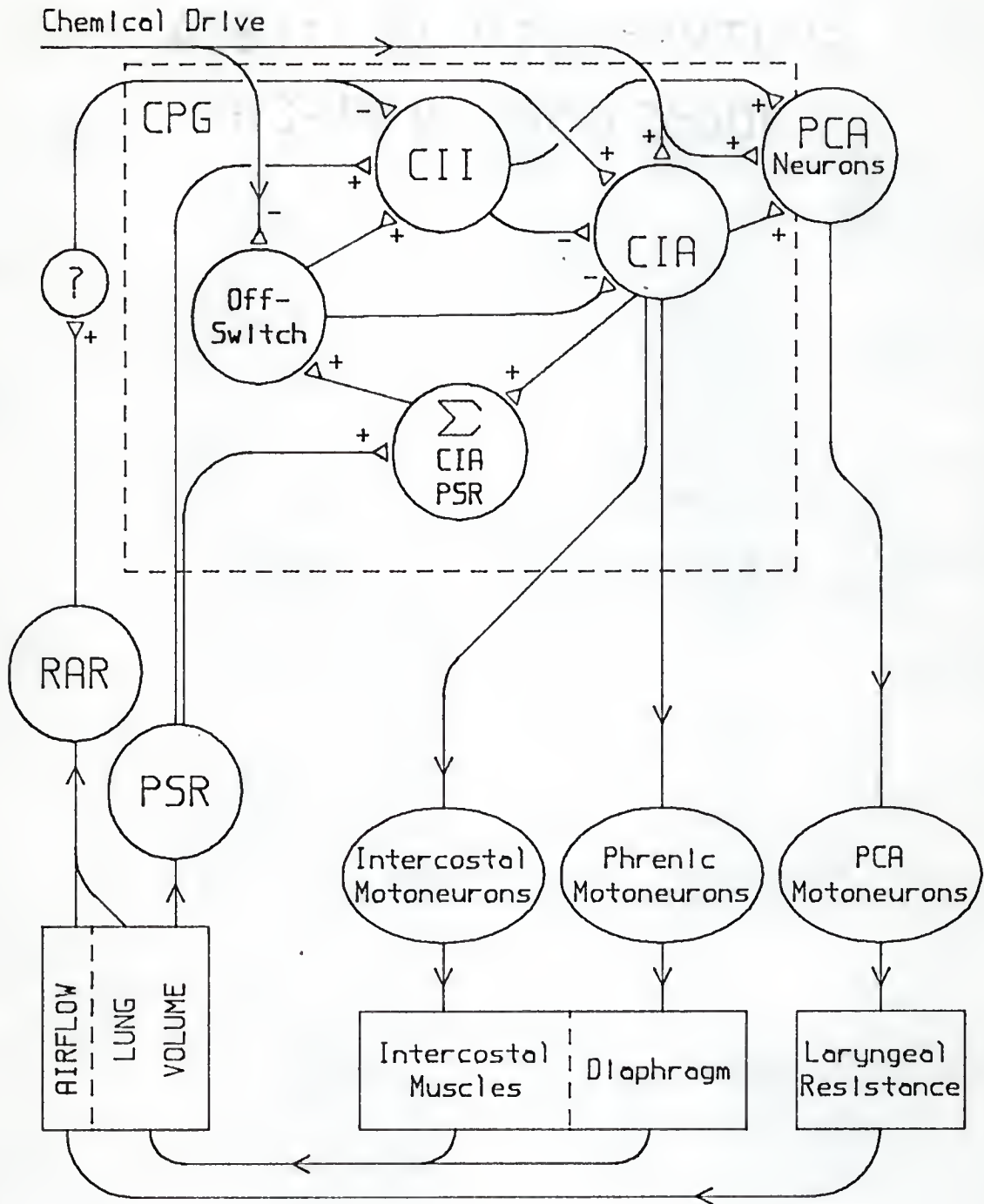


FIGURE 5-9: Proposed Model of Respiratory Control.

Model incorporating PIIA and laryngeal control mechanisms into the model from Figure 5-8.

expiration. Increased lung volume may have an indirect excitatory effect through RAR activation and the CII pool. In infants, the increased V_t associated with CO_2 inhalation and subsequent stimulation of PIIA through RAR feedback may be offset by PSR feedback on the CII pool. This results in the observed insignificant changes in PIIAdi with CO_2 inhalation.

This model proposes that the PCA-controlling neurons are closely tied to the CPG through common neural inputs. The PCA muscle is activated prior to diaphragmatic activation and this timing difference has been shown to be due to earlier activation of laryngeal motoneurons rather than differences in conduction velocities or contraction times (20,89,90). This activation sequence may be the result of fewer interneuronal connections in the laryngeal motoneuron activation pathway or a lower threshold for activation of the laryngeal motoneurons. This model also proposes direct stimulation of laryngeal premotor neurons by increased chemoreceptor feedback. This is consistent with the observation of similar changes in inspPCA and PCAb within individual infants during CO_2 inhalation, and is supported by similar changes in inspiratory and expiratory resistance in hyperoxic cats breathing CO_2 (4). The laryngeal premotor neurons in Figure 5-9 are driven directly by the CIA and CII pools. This means that CO_2 drive stimulation of the CIA pool augments the direct stimulation of the PCA neurons resulting in a greater sensitivity to CO_2 of the laryngeal muscles as compared to the pump muscles.

The observed differences in intercostal and diaphragmatic motor output remain to be addressed. The close association of diaphragmatic and intercostal muscle activity are reflected in a

common source in the CIA integrator of the CPG. The observed difference in the response to CO_2 inhalation may be the result of separate neuronal pools within the CIA integrator that have slightly different inputs from chemoreceptors. Other reasons for the observed responses include different spinal reflexes for the various muscles and changes in pH with hypercapnia that may differentially affect the resting potential of premotor neurons or other interneurons.

Future Studies

These studies emphasize the importance of the control of absolute lung volume to the newborn. Reflex modulation of volume and respiratory cycle timing in the newborn is complex and cannot be thoroughly addressed in a study of this nature. The breathing strategy of the newborn to defend lung volume necessitates future studies where absolute lung volume is measured rather than inferred as in this study. The measurement of lung volume greatly complicates an already complex experimental protocol, but sequential studies on the same infant may help to answer this question. The increase V_t observed with CO_2 inhalation evokes reflex responses of itself. Future studies on reflexes induced by mechanical loading or augmentation would serve to clarify the response to CO_2 breathing. The ability to respond to added mechanical loads could be quite important in the newborn where partial obstruction to airflow can occur from substances in the upper airway, with periodic loss of genioglossus muscle tone, or with spontaneous neck flexion.

Future studies to elucidate the mechanisms behind the CO_2 response of newborns should include varying the level of CO_2 used within an infant to determine if there is a differential response to

a graded drive of the various pump and airflow-controlling muscles. Rebreathing studies in premature infants found different response thresholds for the genioglossus and alae nasi muscles as compared to the diaphragm (18). The present study has shown differences in the response of select muscles to a single level of stimulation, and the response to multiple levels would be useful information.

Studies that address the interaction between chemical and mechanical reflexes could also be performed. Maintained resistive loads could be applied to mimic partial obstruction of the airway. Some studies of this nature with EMG recordings have been done in adult humans (65,77) and both adult (1) and newborn (100) animals, but no information is available from infants. Additionally, single-breath resistive loading could be performed with and without CO_2 breathing to gain more information on mechanical-chemical load interactions. Similar studies have been done on adult humans (102) and animals (44,58), but, once again, not in infants. Experiments of this type could provide valuable information on the control of breathing in the newborn human.

Conclusions

The newborn infant adopts a strategy of breathing to defend absolute lung volume, and this strategy can vary greatly between individuals. Inspiration is controlled through the coordinated activation of pump and UA muscles. The use of P₁IA and active modulation of laryngeal caliber play important roles in controlling expiratory airflow and T_e . The inhalation of CO_2 augments inspiratory activity of the PCA, intercostal and diaphragm muscles to varying degrees in different subjects, although the common result is an elevated V_t with no change in T_i . Expiratory time also remains

unchanged through the combined effects of increased lung recoil pressure, PIIA and laryngeal dilation. The pattern of activation of these muscles depends somewhat on the baseline breathing strategy of the individual. The CO_2 stimulus appears to have a greater effect on the PCA muscles than on the pump muscles, and there is a tendency to stiffen the chestwall through intercostal muscle activation in preference to augmenting diaphragm activation.

In summary, one can conclude from these studies: 1) the newborn infant adopts varied breathing strategies to defend absolute lung volume including the braking of expiration with the diaphragm and laryngeal muscles, 2) the newborn has the ability to augment minute ventilation in a variety of ways when challenged with carbon dioxide, 3) improving diaphragm-ribcage coupling through intercostal muscle activation may provide an energy efficient means of enhancing pump muscle performance, 4) the defense of absolute lung volume is of critical importance to the newborn as demonstrated by the persistence of diaphragmatic braking of expiration throughout this chemical challenge, and 5) the modulation of laryngeal resistance to airflow by posterior cricoarytenoid activation plays a crucial role in the ability of the newborn to respond to a chemical load while maintaining absolute lung volume.

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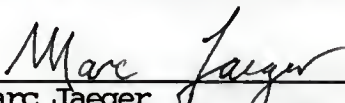
BIOGRAPHICAL SKETCH

John Alexander Wozniak was born in St. Louis, Missouri, on August 27, 1957. He grew up in Mt. Prospect, Illinois, and graduated in 1975 from John Hersey High School, Arlington Heights, Illinois. He received a B.S. degree in electrical engineering from the Massachusetts Institute of Technology, Cambridge, Massachusetts, in 1979. While at M.I.T., he was a member of Delta Tau Delta fraternity and captain of the basketball team. He accepted a position as a biomedical engineer in the College of Veterinary Medicine at the University of Florida in November, 1979. He was accepted as a graduate student in the College of Engineering in 1980 and received a Master of Engineering degree in Electrical Engineering from the University of Florida in 1986. He was admitted to the Department of Physiology in the College of Medicine at the University of Florida in 1983. He was married to Brenda Franey on March 22, 1981. They have two children; Briana Noelle Wozniak, born December 28, 1985, and Alexis Nicole Wozniak, born October 31, 1988.

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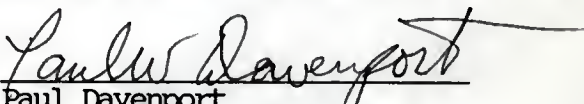
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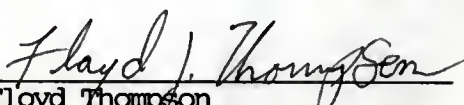
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